ANNALS of ALLERGY

Published by
The American College of Allergists

Volume 9 July-August, 1951 Number 4

# STUDIES IN INFANTILE ECZEMA

## I. Clinical and Statistical Observations on the Allergic Background of 247 Consecutive Cases of Infantile Atopic Dermatitis

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INFANTILE atopic eczema still presents one of the most difficult problems for the dermatologist, the pediatrician, and the allergist. The following statistical observations are reported because they may add to the understanding of this condition. Some of their implications will be discussed in further communications.

These statistics deal almost exclusively with the allergic background of infantile atopic eczema. It is realized that allergic phenomena represent only one side of infantile eczema; other aspects, just as important or, at times, even more so, are not the subject of this paper.

### MATERIAL

Between January 1, 1939, and December 31, 1948, 544 cases of dermatitis in infants up to two years of age were observed. Table I presents the incidence of the various forms. The diagnoses were based on clinical criteria and were made, with few exceptions, by the same observer.

From these figures it becomes apparent that in our material infantile atopic eczema is the most frequent form of eczema in infancy. In evaluating the following statistics one must realize that our material is selected in several ways. Many of our patients with infantile eczema are "second hand" cases, infants who have seen other physicians before. This

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Presented at the Seventh Annual Congress of The American College of Allergists, February 11-14, 1951, Chicago, Illinois.

Approved for publication March 21, 1951.

would seem to account for an accumulation of more difficult and complicated cases. Many of the self-limited cases of contact dermatitis would not reach us. Furthermore, as the role of milk as a causative factor of infantile eczema is well known among the general practitioners, the

TABLE I. INCIDENCE OF DIFFERENT FORMS OF INFANTILE ECZEMA

| | Male | Female | Total |
|---|---|---|---|
| Atopic dermatitis* | 134 | 113 | 247 |
| Atopic dermatitis?** | 38 | 19 | 57 |
| Contact dermatitis*** | 65 | 43 | 108 |
| Seborrheic dermatitis | 59 | 34 | 93 |
| Infectious eczema | 10 | 8 | 18 |
| Miscellaneous eczemas | 10 | 11 | 21 |
| Total | 316 | 228 | 544 |

*Including cases complicated by other forms of eczema.
**In these cases a definite diagnosis could not be established because of insufficient observation or an atypical clinical picture.
***Most cases diagnosed on clinical grounds only.

incidence of milk-sensitive cases in our material is probably below its actual value. Finally, our area covers largely rural areas and smaller cities. This leads to a much higher incidence of contacts with animals than found in the material from large cities, where most statistics in infantile eczema have originated.

Table II, presenting the incidence of positive whealing reactions in the various forms of infantile dermatitis, shows a high percentage of positive scratch tests in atopic dermatitis. There were only a few positive whealing reactions in nonatopic forms of infantile dermatitis. These reactions could be explained in most instances by some other form of allergy, such as rhinitis or asthma.

### REACTORS AND NONREACTORS

These statistics indicate that we have been rather successful in making a clinical diagnosis of infantile atopic dermatitis based on clinical appearance and history, if we accept positive skin tests* as an indication of atopic sensitivity. It is true that only 75 per cent of those classified definitely as atopic dermatitis reacted to scratch tests; this does not mean that the other 25 per cent were not atopic. They just did not give positive reactions to scratch tests. In this group, intradermal tests and passive transfers usually did not elicit positive reactions either. The first category will henceforth be termed "reactors"; the second, "nonreactors."

Individually these nonreacting cases were not different in appearance and course from the reactors. As groups, however, reactors and nonreactors showed marked differences.

*If not specified otherwise, the term *skin tests* in this paper indicates scratch tests. The material used for scratch tests was Lederle's glycerinated extract. For intradermal tests and passive transfers the material from the Arlington Chemical Company was used. The number of scratch tests naturally varied. The minimum was usually the following group of twelve tests: wool, horse, cattle, feathers, dust, kapok, wheat, egg, milk, orange, codfish, Alternaria. In many instances additional tests were carried out as indicated by the child's diet and environment.

Table III shows that the incidence of severe infantile atopic eczema was much higher in the reactor group. However, this applied only to uncom-

TABLE II. INCIDENCE OF POSITIVE WHEALING REACTIONS TO SCRATCH TESTS IN VARIOUS FORMS OF INFANTILE ECZEMA

| | Total | Positive Reactions |
|---|---|---|
| Atopic dermatitis | 231 | 75% |
| Atopic dermatitis? | 49 | 30% |
| Seborrheic dermatitis | 36 | 9% |
| Contact dermatitis<br>Infectious eczema<br>Miscellaneous | 33 | 6% |

TABLE III. SEVERITY OF ECZEMA IN RELATION TO POSITIVE SKIN REACTIONS IN ATOPIC DERMATITIS

| Atopic Dermatitis Uncomplicated | Total | Mild and Moderate | Severe and Very Severe |
|---|---|---|---|
| | | % | % |
| Reactors* | 127 | 39% | 61% |
| Nonreactors | 48 | 85% | 15% |

*The total figures in the various tables are not always identical. This is mainly due to the fact that some cases had to be omitted because of lack of information regarding a specific point.

plicated cases. In those cases which presented a combination of atopic *and* seborrheic dermatitis, about 75 per cent, both of the reactor and nonreactor groups, were mild to moderate. The statistics of Table III have a significant practical application. The incidence of positive scratch tests is highest in the severe-very severe group—about 90 per cent. Thus we get help from skin testing in those cases where it is needed most. In the mild-moderate group, the incidence of positive skin tests is only about 55 per cent.

It is a general experience that even severe atopic infantile eczema affects the health of the infant less than one would expect, although some of these children are in rather poor physical condition. Studies of the hemoglobin values seem to support the general impression. According to the statistics of Table IV, moderate secondary anemia was found not infrequently. However, there was no difference between the average hemoglobin values of the mild-moderate cases and the group containing the severe and very severe cases. Both averages were in agreement with those found in a group of thirty infants suffering from miscellaneous, nonatopic forms of infantile dermatitis.

There were further differences between the reactor and nonreactor groups, the most important being in regard to a different incidence of family histories of allergy, as seen in Table V.

TABLE IV. HEMOGLOBIN VALUES IN ATOPIC INFANTILE ECZEMA

| Age Group (months) | Mild—Moderate Cases | | Severe Cases | | Miscellaneous Forms of Dermatitis | |
|---|---|---|---|---|---|---|
| | Hb. (gm %) | Average | Hb. (gm %) | Average | Hb. (gm %) | Average |
| 1—5 | 9.3—13.5 | 11.6 | 9.7—14.4 | 12.2 | | |
| 6—11 | 9.9—12.9 | 11.6 | 9.3—14.8 | 11.3 | | |
| 12—24 | 7.0—14.7 | 10.7 | 6.4—13.8 | 11.0 | | |
| All ages | 7.0—14.7 | 11.0 | 6.4—14.8 | 11.2 | 7.5—13.5 | 10.9 |

TABLE V. FREQUENCY OF POSITIVE FAMILY HISTORY IN REACTORS AND NONREACTORS

| | Eczema | Urticaria | Asthma | Hay Fever |
|---|---|---|---|---|
| Reactors | 50% | 12% | 21% | 33% |
| Nonreactors | 50% | 12% | 10% | 14% |

TABLE VI. AGE OF ONSET OF INFANTILE ATOPIC DERMATITIS

| Reactors | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Age of Onset | 1 | 2 | 3 | 4 | 5 | 6 | 7/9 | 10/12 | 13/18 | 19/24 | Total |
| Number of cases | 45 | 33 | 23 | 17 | 6 | 6 | 7 | 6 | 3 | 1 | 147 |
| Percentage | 69% | | | 20% | | | 8% | | 3% | | 100% |
| **Non-Reactors** | | | | | | | | | | | |
| Age of Onset | 1 | 2 | 3 | 4 | 5 | 6 | 7/9 | 10/12 | 13/18 | 19/24 | Total |
| Number of cases | 12 | 9 | 10 | 4 | 1 | 4 | 8 | 10 | 6 | 1 | 65 |
| Percentage | 48% | | | 14% | | | 28% | | 10% | | 100% |

This table shows that an equal percentage of children both in the reactor and nonreactor group had a family history of eczema. However, in regard to asthma and hay fever, the story is different. Here the incidence of a positive family history is far greater in the reactor group. There is also a difference in the age of onset between the reactors and nonreactors, as seen in Table VI.

The average age of onset was higher in the nonreacting group.

Table VII shows the types of antigens to which these children reacted by scratch tests.** The table shows that positive reactions to environmental allergens are obtained in over 50 per cent of all infants below six months of age (columns D and E of Table VII). These statistics should correct the often quoted notion that children under one year react to foods only and that environmental allergens play their role only later. However, it is true for our material also that during the first six months of life foods play a greater role than environmental factors, whereas the opposite is the case during the second year of infancy. In our statistics, positive reactions to foods† decreased from 68 per cent during the first five months to 51

**The significance and reliability of these tests will be discussed in another paper.

†Reactions to egg only, without additional reaction to other foods, are excluded. If reactions to egg were counted, the figures would be 85 per cent and 58 per cent, respectively.

TABLE VII. DISTRIBUTION OF REACTIONS TO FOODS AND ENVIRONMENTAL ALLERGENS IN 171 CHILDREN WITH ATOPIC INFANTILE ECZEMA

| | | A | B | C | D | E |
|---|---|---|---|---|---|---|
| Age (month) | Total no. of cases | Positive* reactions to eggs | Egg* only | Foods only | Environmental allergens only | Foods and environmental allergens |
| 1– 5 | 48 | 85% | 17% | 31% | 15% | 37% |
| 6–11 | 78 | 87% | 11% | 17% | 22% | 50% |
| 12–24 | 45 | 49% | 7% | 11% | 42% | 40% |
| All ages | 171 | 77% | 12% | 19% | 25% | 44% |

*In these statistics, reactions to egg were *not* counted as reactions to foods.

TABLE VIII. REACTIONS TO CATTLE AND/OR HORSES IN CHILDREN FROM RURAL AND URBAN AREAS

| | Number of Cases | Cattle, Horse Positive |
|---|---|---|
| Living *on farm* | 75 | 79% |
| *Not* on farm | 73 | 10% |

TABLE IX. INCIDENCE OF POSITIVE SCRATCH TEST REACTIONS IN 166 CASES OF INFANTILE ECZEMA

| Foods | Total Number of Reactions | Environmental Allergens | Total Number of Reactions |
|---|---|---|---|
| Egg | 126 | Cattle | 62 |
| Wheat | 71 | Horse | 53 |
| Potato | 37 | Feathers | 43 |
| Milk | 24 | House dust | 35 |
| Rye | 19 | Wool | 18 |
| Corn | 16 | Dog, ragweed, kapok, goat, orris root, timothy, cat | 5–9 |
| Beef | 13 | | |
| Oats | 12 | | |
| Codfish | 11 | | |
| Asparagus, barley, orange, peanuts | 5–8 | Rabbit, cotton, silk | 2–4 |
| Lamb, pork, rice, peas, chicken, chocolate, tomatoes, apples | 2–4 | | |
| Pear, prunes, beets, carrots, lemon | 1 | | |

per cent during the second year of life. Reactions to environmental allergens increased from 52 per cent in the one to five months group to 82 per cent among the one to two year old group.

The difference between our findings and some of the older literature is to some extent due to selection of our material. Statistics on infantile eczema usually come from urban areas. In our material about one half of the children are from farms.

Table VIII shows the high incidence of positive reactions to farm animals among farmers' children.

The incidence of reacting allergens in our cases is presented in Table IX.

The incidence of reacting foods in Table IX is likely to be influenced by extraneous factors. Most authors report milk as the outstanding allergic factor; in our statistics milk ranks behind wheat and even potatoes in regard to positive reactions. Clinical experience has shown that milk

TABLE X. REACTIONS TO EGG, MILK, WHEAT AND POTATO IN DIFFERENT AGE GROUPS

| Age | Number of Infants | Egg | Milk | Wheat | Potato |
|---|---|---|---|---|---|
| to 3 months | 11 | 100% | 27% | 27% | 9% |
| 3- 4 months | 8 | 88% | 12% | 50% | 25% |
| 4- 5 months | 29 | 83% | 14% | 45% | 22% |
| 6-11 months | 78 | 87% | 17% | 45% | 28% |
| 12-24 months | 45 | 49% | 7% | 33% | 16% |

actually does not play too great a role in our material. The low incidence of milk sensitivity in our cases is probably due to the selective character of our material, as mentioned earlier. Furthermore, as the most important allergens were tested in practically all cases, and the others only in a smaller number, the figures for the less frequently allergenic foods would be actually higher if all infants had been tested with them. Lastly, it must be borne in mind that a reaction to a certain food does not necessarily mean that the child's eczema is connected with this food or even that the child is allergic to this allergen. On the other hand, the child may be highly allergic to a nonreacting food.

Wheat sensitivity seemed the most important allergic factor in our cases. One may question the clinical significance of the positive reactions to wheat. It is well known that a positive reaction to egg white in infantile eczema is found in a high percentage of cases and often does not mean actual sensitivity to eggs. It is assumed that the antibody in this instance may be acquired prenatally, the antigen being transmitted through the placenta. In view of the high rate of reactions to wheat, one may think of a similar explanation in this case. However, the analysis (Table X) of the frequency of sensitivities to various foods in different age groups, indicates that sensitivity to wheat usually is acquired by the infant *after* birth. Clinical experience also demonstrated that wheat was actually the most important food allergen in infantile atopic eczema.

## SUMMARY

1. Statistics on 247 consecutive cases of infantile atopic dermatitis in an essentially rural area are reported.

2. Seventy-five per cent gave positive whealing reactions to scratch tests.

3. In general, positive food reactions were more frequent during the first six months; and environmental allergens played their greatest role after that age.

4. However, even during the first half year of life, reactions to environmental allergens were found in more than 50 per cent.

5. The high incidence of positive reactions to environmental allergens is due partly to the large percentage of farmers' children in our material—79 per cent of the latter reacted to cattle and/or horse dander.

6. Egg, wheat, potato, and milk gave the most frequent food reactions, in that order.

7. Cattle, horse, feathers, house dust, and wool were the most common reactors among the environmental allergens.

8. Reactions to egg decreased from 100 per cent during the first three months to 49 per cent during the second year of life. Reactions to wheat and potatoes occurred in 27 per cent and 9 per cent, respectively, of infants up to three months, and increased to about 45 per cent and 25 per cent, respectively, during the remainder of the first year of life.

9. There were several differences between those atopic infants that gave positive scratch test reactions (reactors) and those who did no (nonreactors): (a) the eczema was usually less severe in the nonreactor group; (b) the incidence of a positive family history of hay fever and/or asthma was twice as great in the reactor group; (c) the age of onset of the eczema was slightly higher in the nonreactor group.

## DISCUSSION

DR. JEROME GLASER: Dr. Epstein's concise presentation brings out many interesting points. It is highly significant that his observations refute the statement of Cooke to the effect that the direct skin test with the wheal type of reaction is of no practical value. Dr. Epstein therefore corroborates the observations of practically all men specializing in pediatric allergy. As regards children who do not give positive skin tests, my experience has been that if the disease continues positive skin tests eventually develop. Table 7 confirms Dr. Hill's observations that 55 per cent of children who react to anything react to egg white. Dr. Epstein's presentation clearly indicates that the allergens to which a child may become sensitive depends upon the "climate" of the child. The allergens to which one is exposed on a farm may differ significantly from those to which the same child may be exposed to in an urban environment. The frequency of sensitization to wheat which Dr. Epstein points out in early childhood highlights the importance of not starting infants in potentially allergic families on wheat cereal. His incidence of positive reactions to potato is most interesting. I see these reactions and occasionally they are clinically significant. I recall that Dr. Hill, some years ago, stated that he had never seen a positive reaction to the potato which was of clinical importance.

I should like to ask Dr. Epstein if he has ever seen a child under the age of one year with a positive skin test to egg white who is not also clinically sensitive to egg white. I, personally, never have.

DR. STEPHAN EPSTEIN: I cannot answer Dr. Glaser's question because I eliminate eggs routinely in all instances of infantile eczema. As a rule, I do not try eggs until the child is one year of age. At that time some of the children who give a positive reaction to eggs seem to tolerate them; however, this does not exclude the fact that these infants may also have been clinically sensitive to eggs at an earlier stage. Clinical experience, with both intentional and unintentional feeding of eggs, has convinced me that at least some of the infants with positive egg reactions are clinically sensitive to this food, some of them extremely so.

# FUNGUS ALLERGY

## I. Incidence of Atmospheric Spores in the Los Angeles Area

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A COMPREHENSIVE survey of the atmospheric incidence of pollens and of fungus spores in this area was begun by one of us (A. M. T.) in 1940. The results of the pollen survey covering the five-year period 1941-1945 have already appeared in this journal.[10] This paper presents the results of the fungus spore survey carried out by both plate and slide exposures. The slide data were accumulated in conjunction with the pollen survey and cover the same five-year period from January 1, 1941 to December 31, 1945. Plate exposures were initiated May 1, 1940, and terminated June 30, 1945.

### METHOD

Standard size (9 cm diameter) Petri dishes containing Sabouraud's medium were exposed daily for thirty minutes to the outdoor atmosphere. The place of exposure was a window sill on the ninth floor of an office building in the Westlake Park (now renamed MacArthur Park) area. The time of exposure was between 3:00 and 4:00 p.m. Since the window was so constructed as to swing on a horizontal axis, the lower half could be pushed out to form a protective covering when it rained. The plates were kept at room temperature. By the fourth or fifth day following exposure, discrete colonies were visible to the naked eye. At this time identification was made of the small colonies with little or no mycelium (actinomycetes, yeasts, et cetera) that were apt to be overgrown later on. By the eighth to the tenth day, the expanding mycelial growths had usually developed spores admitting of identification. Colonies that could not be identified at this time were encircled with wax pencil on the reverse of the plate and allowed to remain up to three weeks, at which time either final identification was made or they were recorded as sterile. Identification was made by gross and microscopic examination. Species identification was not attempted, and some groupings were made beyond generic boundaries. For example, the term "actinomycetes" in this paper covers both of the aerobic genera *Nocardia* and *Streptomyces* in accordance with recent classification.* Of the two genera, the latter was by far the more predominant. The term yeasts is exclusive of the pigmented *Rhodotorula* but includes *Cryptococcus* and *Candida* as well as the true ascosporogenic yeasts. The term *Penicillium* covers also *Paecilomyces* and *Gliocladium*. *Acrothecium*

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*See footnote on opposite page.

TABLE I. FUNGI IDENTIFIED IN SURVEY. BOLD FACE TYPE INDICATES FREQUENT OCCURRENCE

| | | |
|---|---|---|
| 1. Acremoniella | 21. Gloeosporium | 42. Sclerotinia |
| 2. Acremonium | 22. Helminthosporium | 43. **Scopulariopsis** |
| 3. Acrostalagmus | 23. Hormodendrum | 44. **Sepedonium** |
| 4. **Acrothecium** | 24. Hyphoderma | 45. Septonema |
| 5. **Actinomycetes** | 25. **Macrosporium** | 46. Sphaeropsis |
| 6. **Alternaria** | 26. **Monilia** | 47. Spondyiocladium |
| 7. Arthrobotrys | 27. Monosporium | 48. Sporobolomyces |
| 8. Aspergillus | 28. **Mucor** | 49. Sporodesmus |
| 9. **Botrytis** | 29. Mycoderma | 50. **Stachybotrys** |
| 10. **Cephalosporium** | 30. **Nigrospora** | 51. **Stemphylium** |
| 11. Cephalothecium | 31. Papularia | 52. Stigmella |
| 12. Cercospora | 32. Penicillium | 53. Stilbella |
| 13. **Chaetoconidium** | 33. Pestalozzia | 54. Stysanus |
| 14. **Chaetomium** | 34. **Phoma** | 55. Titaea |
| 15. Coryneum | 35. Plenozythia | 56. Trichoderma |
| 16. **Epicoccum** | 36. **Pleospora** | 57. Trichosporon |
| 17. Eurotium | 37. **Pullularia** | 58. Tubercularia |
| 18. **Fusarium** | 38. Pythium | 59. Verticillium |
| 19. Fusidium | 39. **Rhizopus** | 60. Yeasts |
| 20. Geotrichum | 41. Rossellinia | 61. Zygodesmus |
| | 40. **Rhodotorula** | |

was not tabulated separately but was included in *Helminthosporium*. *Pleospora,* the perfect form of *Macrosporium,* was frequently noted in association with the latter but no attempt was made to keep a separate count for it. *Monilia* occurred for the most part as *M. sitophila,* overgrowing the plate, occasionally as *M. cinerea* and similar saprophytic species forming small definite colonies.

Sterile colonies occurred no more than one or two to a plate and no more than approximately ten per month. Subculture of these at the beginning of the study did not, when successful, produce any forms other than those identifiable without subculturing; hence the procedure was soon stopped because of the added labor involved.

All counts for each genus or broader grouping were totaled by months. Where a plate was contaminated or a slide spoiled, the resultant actual total for the month was recalculated by simple proportion to a theoretical total. Since such accidents did not occur more than once or twice a month, and not in every month, no substantial error was introduced, and any deviation from the actual was thereby confined to that particular month.

Slide counts of *Alternaria, Helminthosporium* (and *Acrothecium), Hormodendrum,* rusts and smuts were carried out as part of the pollen survey mentioned above. The place of exposure of the slides was a residential area a few miles northwest of the office building. As mentioned in the pollen survey, the counts were based on an area of two square centi-

*Some names that have in the past been applied to all or part of this group of organisms are as follows: *Actinobacillus, Actinocladothrix, Actinomyces, Cladothrix, Discomyces, Leptothrix, Oospora, Oidium, Microsiphonales, Nocardia, Proactinomyces,* and *Streptothrix.* To end this confusion, Waksman and Henrici have proposed a new classification (Waksman, S. A., and Henrici, A. T.: The Nomenclature and Classification of the Actinomycetes, Journal of Bacteriology, 46:337, October, 1943) which is now incorporated into Bergey's *Manual of Determinative Bacteriology,* 6th ed., 1948. In this classification the term *Actinomyces* is restricted solely to the generic name of the anaerobic, pathogenic species; *Nocardia* becomes the generic name for the aerobic, fragmenting, nonsporulating types; and *Streptomyces* covers the aerobic, sporulating types.

TABLE II. SUMMARY OF PLATE COUNTS OF MOST FREQUENTLY OCCURRING FUNGI

| | Total Number Colonies May, 1940 through June, 1945 | Number of Months in which Appearance Was Made | Average Monthly Number of Colonies | Per Cent of Monthly Total | Average Yearly Count Based on 4 Complete Calendar Years 1941-1944 | Per Cent of Yearly Total |
|---|---|---|---|---|---|---|
| 1. Hormodendrum | 39,572 | 62 | 628 | 53.8 | 7078 | 53.8 |
| 2. Alternaria | 10,491 | 62 | 167 | 14.3 | 1950 | 14.8 |
| 3. Actinomycetes | 4,628 | 62 | 75 | 6.4 | 953 | 7.2 |
| 4. Epicoccum | 2,664 | 62 | 42 | 3.6 | 474 | 3.6 |
| 5. Pullularia | 2,584 | 62 | 41 | 3.5 | 501 | 3.8 |
| 6. Penicillium | 2,470 | 62 | 39 | 3.3 | 438 | 3.4 |
| 7. Yeasts | 2,130 | 62 | 34 | 2.9 | 427 | 3.2 |
| 8. Rhodotorula | 1,439 | 62 | 23 | 2.0 | 277 | 2.1 |
| 9. Macrosporium | 1,086 | 62 | 17 | 1.5 | 195 | 1.4 |
| 10. Aspergillus | 802 | 62 | 13 | 1.1 | 171 | 1.3 |
| 11. Stemphylium | 718 | 62 | 12 | 1.0 | 127 | .9 |
| 12. Helminthosporium | 643 | 61 | 11 | .9 | 111 | .8 |
| 13. Fusarium | 613 | 61 | 10 | .9 | 69 | .5 |
| 14. Phoma | 498 | 59 | 9 | .8 | 87 | .6 |
| 15. Botrytis | 482 | 61 | 8 | .7 | 98 | .7 |
| 16. Cephalosporium | 444 | 57 | 8 | .7 | 81 | .6 |
| 17. Scopulariopsis | 308 | 54 | 6 | .5 | 64 | .5 |
| 18. Chaetoconidium | 161 | 29 | 6 | .5 | 40 | .4 |
| 19. Mucor | 132 | 46 | 3 | .3 | 20 | .2 |
| 20. Monilia | 130 | 36 | 4 | .3 | 17 | .1 |
| 21. Sepedonium | 111 | 32 | 3 | .3 | 23 | .2 |
| 22. Nigrospora | 93 | 32 | 3 | .3 | 23 | .2 |
| 23. Rhizopus | 90 | 44 | 2 | .2 | 15 | .1 |
| 24. Chaetomium | 60 | 37 | 2 | .2 | 13 | .1 |
| 25. Stachybotrys | 38 | 26 | 1 | .1 | 8 | .1 |
| Totals | | | 1,167 | | 13,260 | |

meters. It should be noted here that in counting *Hormodendrum* each clump was counted as a single spore; the implications of this will be discussed below.

## RESULTS

Table I is an alphabetical list of all fungi identified on the plates. A few, such as *Sphaeropsis* and *Mycoderma,* were seen only once or twice during the entire period of the survey. The others scale upwards from this level of incidence. The most frequently encountered organisms are indicated by bold face type.

Pertinent data regarding the latter group are summarized in Table II, which lists twenty-five different genera or families. The total count for each of these, over the entire period from May 1, 1940, through June 30,

1945, is given in the first column of figures. The second column reveals the actual number of months during which each genus or family appeared; and the third column, the average number of colonies per month in descending order of frequency.

Since the beginning and end of the survey by the plate method do not coincide with the calendar year, to obtain the average yearly totals shown in column 5 the data for only the four full calendar years from January 1, 1941, through December 31, 1944, were used. The relative frequency of occurrence based on this yearly average over a four-year period differs but little from that based on the monthly average for the five-year period, as can be seen by comparing columns 4 and 6. (In either instance there is a slight margin of error affecting the absolute but not relative percentage values due to ignoring both sterile and infrequently appearing fungi, but the total of such colonies would approximate no more than about fifteen per month. Also, the limitation of a monthly "average" as an indicator of atmospheric incidence must be kept in mind in the case of those fungi having marked seasonal fluctuations.)

Using either the monthly or yearly average as a measure of frequency of occurrence, it can be said that *Hormodendrum* constitutes slightly more than half (54 per cent) of all colonies and is almost four times as abundant in the atmosphere as *Alternaria.* The latter forms approximately one-seventh (14 per cent) of all colonies. The two combined comprise about two-thirds (68 per cent) of all colonies. The eleven different types of organisms next in frequency (actinomycetes, *Epicoccum, Pullularia, Penicillium,* yeasts, *Rhodotorula, Macrosporium, Aspergillus, Stemphylium, Helminthosporium,* and *Fusarium)* together constitute no more than about one-fourth (28 per cent) of all colonies. The remaining twelve genera form less than one-twentieth (5 per cent) of the total. If instead of listing the non-pigmented yeasts and *Rhodotorula* separately the two be combined, the yeast family comes to rank fourth in frequency between the actinomycetes and *Epicoccum.* The non-pigmented yeasts outnumber *Rhodotorula* in the ratio of 3 to 2.

Table III presents information regarding monthly variations in colony counts. In part A the monthly counts for each year are given for *Alternaria, Helminthosporium,* and *Hormodendrum* to afford comparison with the slide counts. To conserve space only the five-year monthly averages are given for the other organisms in Part B, but approximate quantitative information for each year is presented through the medium of the graphs of Figure 1.

Table IV summarizes the slide count data. *Alternaria* spores were the ones most frequently encountered on the slides, forming rather consistently from year to year about 40 per cent of all spores. The fact that *Alternaria* outnumbered *Hormodendrum* on the slides in contrast to the situation on the plates will be discussed below. *Hormodendrum* was second in frequency during the last two years but was outnumbered by the rusts the

TABLE III. MONTHLY PLATE COUNTS, MAY, 1940, THROUGH JUNE, 1945

**Part A—Monthly Totals Each Year**

| | Year | Jan. | Feb. | March | April | May | June | July | August | Sept. | Oct. | Nov. | Dec. | Total for Year |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Alternaria | 1940 | | | | | 372 | 199 | 225 | 143 | 146 | 206 | 210 | 157 | |
| | 1941 | 95 | 45 | 86 | 101 | 295 | 210 | 211 | 176 | 128 | 174 | 275 | 145 | 1941 |
| | 1942 | 109 | 131 | 163 | 284 | 252 | 154 | 168 | 198 | 141 | 140 | 233 | 127 | 2100 |
| | 1943 | 148 | 115 | 144 | 193 | 194 | 209 | 192 | 209 | 178 | 172 | 274 | 154 | 2182 |
| | 1944 | 95 | 110 | 114 | 121 | 143 | 109 | 158 | 148 | 143 | 134 | 179 | 124 | 1578 |
| | 1945 | 128 | 147 | 154 | 113 | 166 | 131 | | | | | | | |
| | Average | 115 | 110 | 132 | 162 | 237 | 169 | 191 | 175 | 147 | 165 | 234 | 141 | |
| Helminthosporium | 1940 | | | | 10 | 10 | 14 | 32 | 35 | 26 | 25 | 7 | 5 | |
| | 1941 | 4 | | 4 | 8 | 13 | 17 | 7 | 4 | 4 | 6 | 12 | 3 | 82 |
| | 1942 | 3 | 4 | 5 | 4 | 8 | 8 | 19 | 23 | 25 | 15 | 10 | 1 | 125 |
| | 1943 | 15 | 3 | 7 | 9 | 11 | 18 | 25 | 16 | 18 | 21 | 11 | 3 | 157 |
| | 1944 | | 1 | 4 | 4 | 7 | 6 | 14 | 18 | 10 | 6 | 9 | 4 | 82 |
| | 1945 | 7 | 1 | 4 | 5 | 7 | 9 | | | | | | | |
| | Average | 7 | 2 | 5 | 7 | 9 | 12 | 19 | 19 | 17 | 15 | 10 | 3 | |
| Hormodendrum | 1940 | | | | | 947 | 569 | 492 | 526 | 653 | 1378 | 990 | 590 | |
| | 1941 | 441 | 212 | 209 | 230 | 522 | 457 | 450 | 392 | 499 | 708 | 846 | 317 | 5283 |
| | 1942 | 188 | 248 | 328 | 392 | 416 | 396 | 427 | 615 | 600 | 836 | 841 | 453 | 5740 |
| | 1943 | 513 | 233 | 314 | 521 | 779 | 552 | 580 | 905 | 932 | 1265 | 1646 | 846 | 9086 |
| | 1944 | 367 | 316 | 301 | 678 | 1047 | 644 | 673 | 745 | 671 | 1005 | 1061 | 693 | 8201 |
| | 1945 | 760 | 537 | 582 | 575 | 1163 | 814 | | | | | | | |
| | Average | 454 | 309 | 347 | 479 | 812 | 572 | 524 | 637 | 671 | 1038 | 1077 | 580 | |

TABLE III. (CONTINUED)

**Part B—Five-Year Averages**

| | January | February | March | April | May | June | July | August | September | October | November | December |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Actinomycetes | 35 | 32 | 43 | 46 | 86 | 93 | 136 | 129 | 108 | 87 | 48 | 38 |
| Alternaria | 115 | 110 | 132 | 162 | 237 | 169 | 191 | 175 | 147 | 165 | 234 | 141 |
| Aspergillus | 6 | 4 | 5 | 4 | 4 | 11 | 19 | 26 | 27 | 22 | 21 | 9 |
| Botrytis | 8 | 9 | 13 | 16 | 8 | 7 | 8 | 4 | 7 | 4 | 4 | 7 |
| Cephalosporium | 3 | 5 | 4 | 4 | 4 | 6 | 9 | 14 | 15 | 14 | 7 | 7 |
| Chaetoconidium | 4 | 2 | 6 | 6 | 9 | 7 | 7 | 8 | 6 | 2 | 2 | 4 |
| Chaetomium | 1 | 2 | 1 | 1 | 2 | 1 | 1 | 1 | 1 | 2 | 2 | 2 |
| Epicoccum | 25 | 15 | 25 | 56 | 98 | 68 | 47 | 38 | 25 | 31 | 36 | 25 |
| Fusarium | 5 | 3 | 8 | 8 | 12 | 12 | 17 | 13 | 15 | 14 | 6 | 6 |
| Helminthosporium | 7 | 2 | 5 | 7 | 9 | 12 | 19 | 19 | 17 | 15 | 10 | 3 |
| Hormodendrum | 454 | 309 | 347 | 479 | 812 | 572 | 524 | 637 | 671 | 1038 | 1077 | 580 |
| Macrosporium | 10 | 11 | 12 | 20 | 25 | 20 | 14 | 22 | 18 | 23 | 18 | 12 |
| Monilia | 4 | 3 | 3 | 3 | 3 | 5 | 4 | 1 | 2 | 3 | 4 | 2 |
| Mucor | 2 | 2 | 3 | 5 | 3 | 2 | 3 | 3 | 3 | 2 | 2 | 4 |
| Nigrospora | 2 | 0 | 0 | 0 | 1 | 4 | 3 | 5 | 5 | 3 | 3 | 2 |
| Penicillium | 38 | 30 | 31 | 33 | 31 | 38 | 53 | 54 | 47 | 42 | 47 | 33 |
| Phoma | 7 | 7 | 13 | 20 | 10 | 12 | 4 | 5 | 2 | 6 | 5 | 10 |
| Pullularia | 52 | 43 | 72 | 49 | 32 | 22 | 17 | 18 | 25 | 40 | 64 | 61 |
| Rhizopus | 1 | 1 | 1 | 3 | 2 | 2 | 2 | 2 | 5 | 3 | 2 | 1 |
| Rhodotorula | 27 | 24 | 30 | 29 | 20 | 17 | 16 | 19 | 14 | 25 | 29 | 30 |
| Scopulariopsis | 3 | 3 | 3 | 1 | 5 | 7 | 7 | 8 | 10 | 7 | 7 | 5 |
| Sepedonium | 3 | 2 | 5 | 2 | 5 | 5 | 4 | 4 | 4 | 3 | 1 | 2 |
| Stemphylium | 13 | 8 | 12 | 14 | 14 | 11 | 10 | 8 | 7 | 12 | 22 | 10 |
| Stachybotrys | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 3 | 1 | 1 | 1 |
| Yeasts | 43 | 38 | 49 | 45 | 35 | 18 | 11 | 17 | 16 | 36 | 50 | 52 |
| Average Total All Fungi | 869 | 679 | 835 | 1016 | 1468 | 1122 | 1131 | 1231 | 1204 | 1613 | 1716 | 1031 |

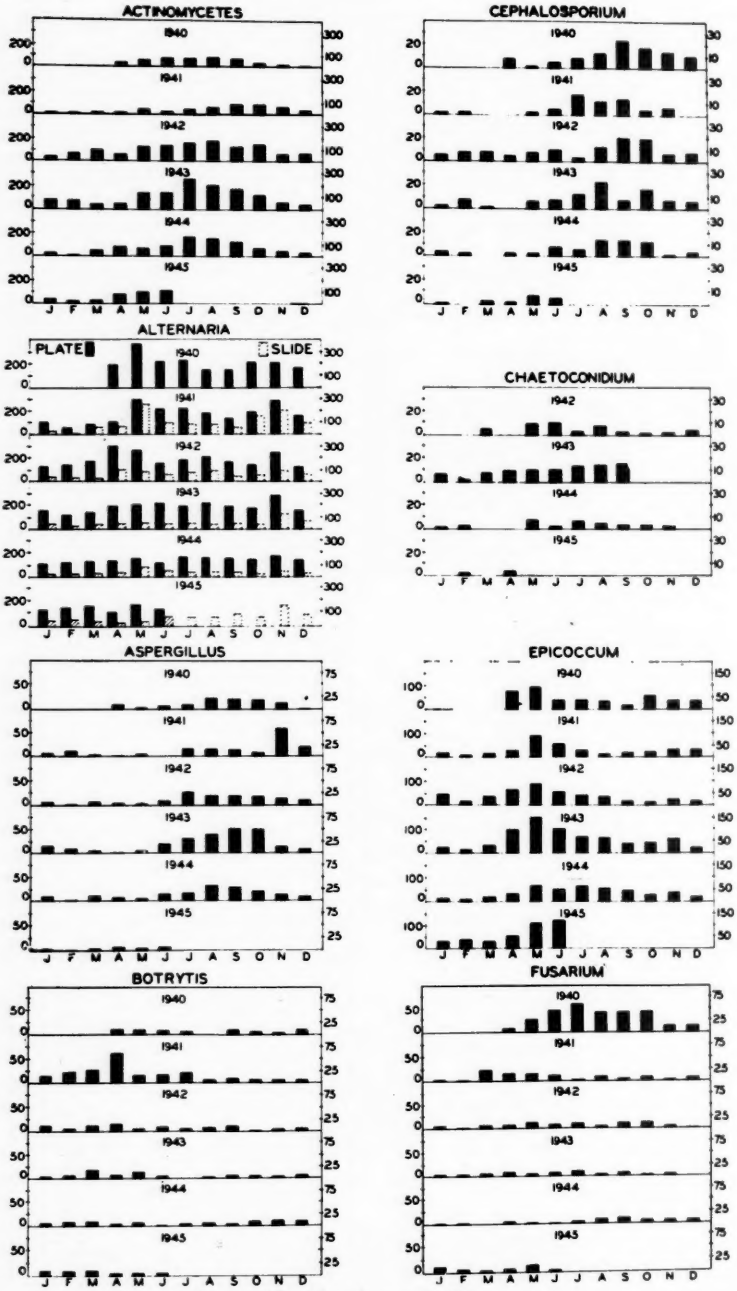


Fig. 1. Monthly plate and slide counts.

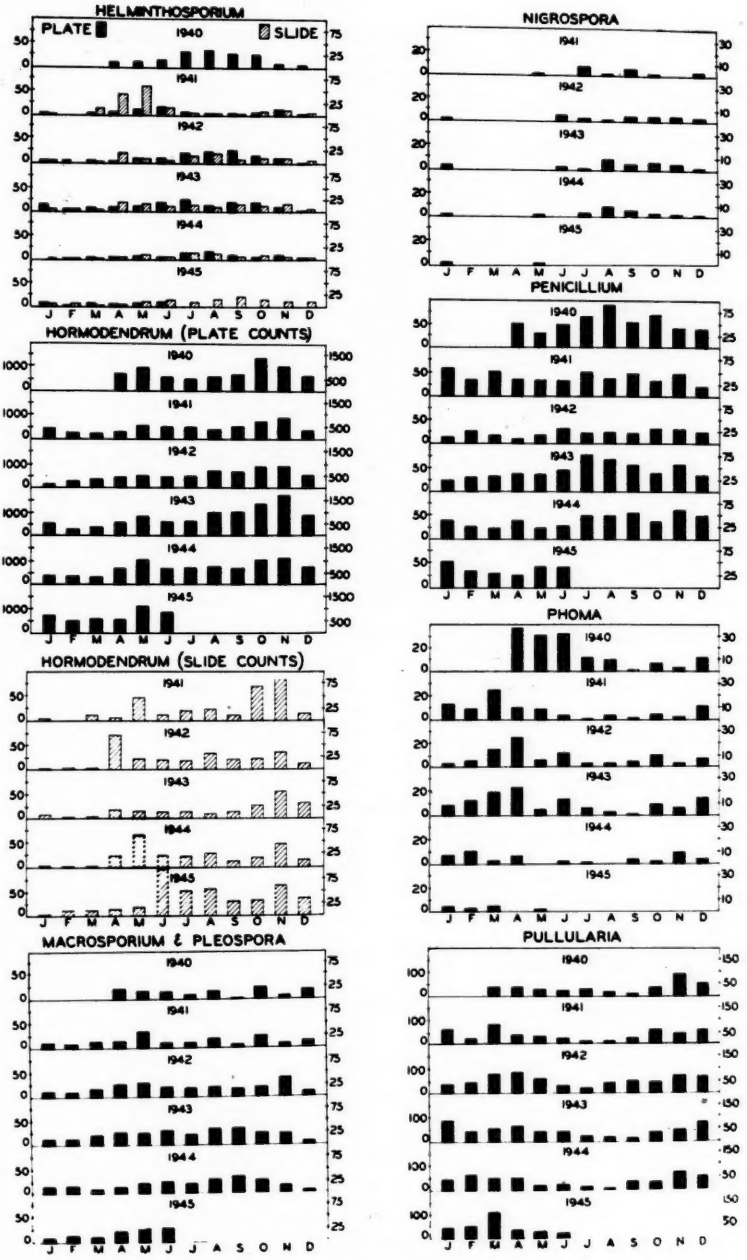


Fig. 1. (continued).

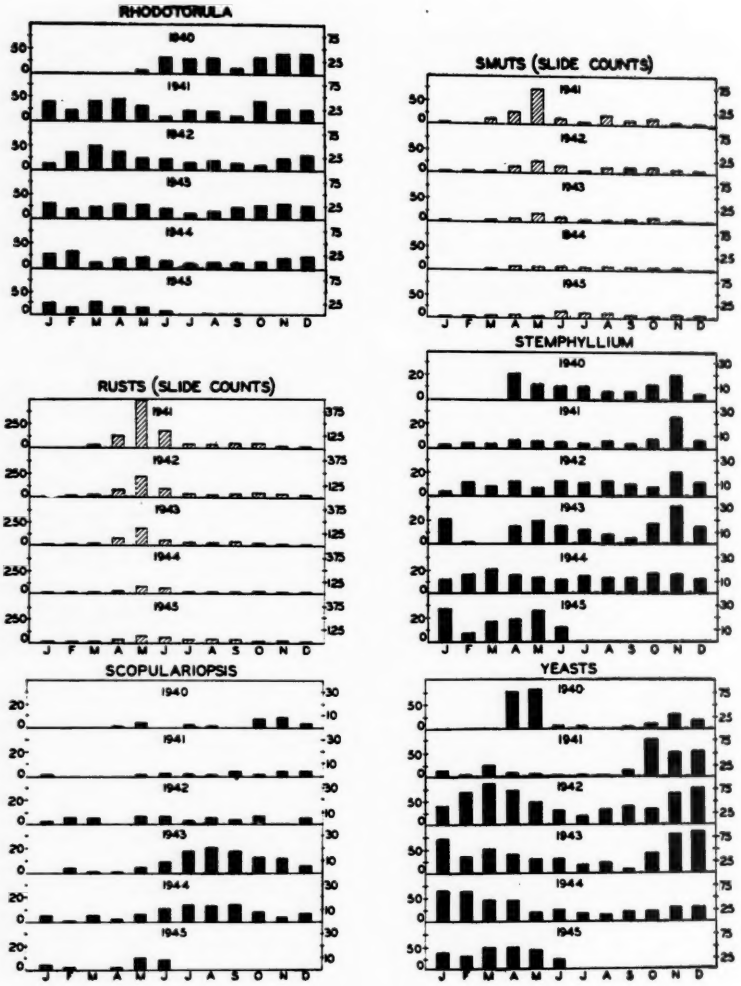


Fig. 1. (concluded)

first three years. Conversely, the rusts ranked next to *Alternaria* during the first three years, but dropped to third for the next two. *Helminthosporium* ranked fourth each year and the smuts last.

In Figure 1 are arranged alphabetically the graphs of both plate and slide counts of most of the organisms listed in Table II with the addition of the rusts and smuts. (To conserve space we have omitted the charts of *Chaetomium, Monilia, Mucor, Rhizopus, Scpedonium,* and *Stachybotrys,* since all of these are more or less identical in showing a non-seasonal pat-

tern of occurrence at a rather low level compard with the others.) It can be seen from examination of the graphs (good correspondence between plate and slide counts may be noted) that it is possible to divide the fungi into three groups in accordance to whether they are present year round with no seasonal change in level of incidence, or exhibit an increase in incidence during either the winter rainy season or the summer dry season. The latter group may be further subdivided in accordance to whether the organisms attain definite peaks of incidence during certain months. The specific organisms falling into each group are shown in Table V. For some organisms whose fluctuations are not marked, e. g., *Botrytis* or *Fusarium,* the present position in the table is to be regarded as tentative, to be confirmed or changed by further accumulation of data. On the other hand, what is apparently a definite seasonal variation of such a form as *Aspergillus* may in future surveys be altered by changes in host factors which may occur in the interim.

Of particular interest is the subgroup made up of *Epicoccum, Hormodendrum,* and three members of the Alternaria tribe: *Alternaria, Macrosporium,* and *Stemphylium.* This group reveals a definite tendency to exhibit two peaks of incidence during the year, one in spring and one in fall. The characteristics of this twin peak pattern may be summarized as follows: (1) both spring and fall peaks tend to be present each year, but in some years either peak may be absent; (2) when simultaneously present, either peak may be the larger one; (3) the spring peak usually takes place in May but may shift to, or expand to take in, either April or June; (4) the fall peak tends to occur in November but may shift to, or expand to take in, either October or December. Exceptions to these generalizations are seen in the case of *Macrosporium,* where the fall peak occurred in September in 1943 and 1944; and *Stemphylium,* where unusually large counts were obtained in January of both 1943 and 1945.

Figure 2 shows that the average curve of incidence of the total fungus spore population in the air begins with a low point in February, then rises in succeeding months to a peak in May; a recession from this peak occurs in June and July to some extent, though counts still remain high; another rise then takes place to a second (and from the present data, the greater) peak in November; recession then occurs to the winter low. It is clear that this curve is determined primarily by the additive effects of *Hormodendrum* and *Alternaria.* If the five-year average counts of these two and of the "winter prevalent" group of organisms (Group II of Table V) be subtracted from the total, the remaining organisms show a curve of incidence which closely follows the annual temperature curve and is obviously a reflection of the total of the "summer prevalent" group (Group III) masking the total of the perennially static group (Group I).

Figure 3 is a graph of the monthly slide counts based on the five-year average. Here too the spring and fall peaks of *Alternaria* and *Hormodendrum* are evident. Reference to Table IV shows that the spring peaks of

TABLE IV. SLIDE COUNTS OF SPORES PER 2 SQ CM

| | Year | Jan. | Feb. | March | April | May | June | July | Aug. | Sept. | Oct. | Nov. | Dec. | Total For Year | Per Cent of All Spores for Year |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Alternaria | 1941 | 14 | 6 | 48 | 65 | 251 | 90 | 78 | 83 | 56 | 155 | 212 | 95 | 1153 | 41.2 |
| | 1942 | 33 | 20 | 16 | 96 | 82 | 47 | 59 | 91 | 46 | 47 | 95 | 57 | 689 | 41.5 |
| | 1943 | 46 | 23 | 24 | 39 | 43 | 44 | 42 | 39 | 47 | 48 | 126 | 71 | 592 | 42.0 |
| | 1944 | 17 | 8 | 12 | 34 | 75 | 41 | 33 | 45 | 32 | 28 | 48 | 23 | 396 | 39.3 |
| | 1945 | 33 | 52 | 24 | 13 | 39 | 79 | 63 | 76 | 96 | 74 | 158 | 92 | 799 | 48.6 |
| | Total | 143 | 109 | 124 | 247 | 490 | 301 | 275 | 334 | 277 | 352 | 639 | 338 | 3629 | |
| | Average | 29 | 22 | 25 | 49 | 98 | 60 | 55 | 67 | 55 | 70 | 128 | 68 | 726 | 42.5 |
| Helminthosporium | 1941 | 3 | | 15 | 44 | 64 | 15 | 5 | 4 | 3 | 8 | 10 | 4 | 175 | 6.3 |
| | 1942 | 3 | | 1 | 21 | 7 | 5 | 14 | 19 | 6 | 10 | 10 | 5 | 101 | 6.1 |
| | 1943 | 6 | 3 | 5 | 18 | 13 | 14 | 17 | 10 | 16 | 13 | 17 | 9 | 141 | 10.0 |
| | 1944 | 1 | 1 | 2 | 4 | 8 | 6 | 14 | 12 | 6 | 9 | 6 | 4 | 73 | 7.3 |
| | 1945 | 6 | 5 | 1 | 3 | 8 | 15 | 8 | 14 | 19 | 13 | 9 | 9 | 110 | 6.7 |
| | Total | 19 | 9 | 24 | 90 | 100 | 55 | 58 | 59 | 50 | 53 | 52 | 31 | 600 | |
| | Average | 4 | 3 | 5 | 16 | 20 | 11 | 12 | 12 | 10 | 11 | 10 | 6 | 120 | 7.3 |
| Hormodendrum | 1941 | 2 | | 11 | 6 | 48 | 11 | 22 | 23 | 10 | 67 | 85 | 13 | 298 | 10.7 |
| | 1942 | 1 | 3 | 2 | 72 | 23 | 20 | 19 | 33 | 18 | 22 | 35 | 13 | 261 | 15.7 |
| | 1943 | 7 | 3 | 4 | 19 | 14 | 13 | 13 | 8 | 13 | 25 | 55 | 32 | 206 | 14.6 |
| | 1944 | 4 | 2 | 2 | 24 | 66 | 25 | 22 | 28 | 11 | 19 | 46 | 14 | 2 53 | 26.1 |
| | 1945 | 4 | 12 | 10 | 13 | 34 | 94 | 51 | 51 | 28 | 30 | 62 | 37 | 429 | 26.1 |
| | Total | 18 | 20 | 29 | 134 | 185 | 163 | 127 | 146 | 80 | 163 | 283 | 109 | 1457 | |
| | Average | 4 | 4 | 6 | 27 | 37 | 33 | 25 | 29 | 16 | 33 | 57 | 22 | 291 | 18.6 |
| Rusts | 1941 | | | 29 | 129 | 491 | 178 | 36 | 27 | 47 | 45 | 18 | 14 | 1017 | 36.3 |
| | 1912 | 2 | 9 | 19 | 63 | 205 | 80 | 27 | 16 | 26 | 35 | 25 | 14 | 521 | 31.4 |
| | 1913 | 11 | 4 | 14 | 67 | 164 | 47 | 25 | 21 | 33 | 21 | 9 | 7 | 426 | 30.2 |
| | 1914 | 4 | 5 | 4 | 26 | 66 | 46 | 11 | 13 | 14 | 28 | 11 | 8 | 236 | 23.4 |
| | 1945 | 6 | 5 | 5 | 34 | 63 | 35 | 26 | 19 | 22 | 14 | 14 | 7 | 250 | 15.2 |
| | Total | 23 | 23 | 71 | 319 | 992 | 386 | 125 | 96 | 142 | 146 | 77 | 50 | 2 50 | |
| | Average | 6 | 6 | 14 | 61 | 198 | 77 | 25 | 19 | 28 | 29 | 15 | 10 | 490 | 27.3 |
| Smuts | 1941 | 1 | | 9 | 23 | 71 | 11 | 4 | 17 | 6 | 10 | 2 | 1 | 155 | 5.5 |
| | 1942 | 1 | 1 | 1 | 11 | 22 | 12 | 3 | 10 | 10 | 9 | 6 | 2 | 88 | 5.3 |
| | 1943 | 1 | | 1 | 4 | 17 | 8 | 3 | 2 | 3 | 6 | 1 | | 46 | 3.2 |
| | 1944 | | | 1 | 7 | 5 | 5 | 5 | 5 | 4 | 4 | 3 | | 39 | 3.9 |
| | 1945 | 2 | 2 | 3 | 5 | 2 | 12 | 9 | 8 | 4 | 2 | 4 | 2 | 55 | 3.4 |
| | Total | 5 | 3 | 15 | 50 | 117 | 48 | 24 | 42 | 27 | 31 | 16 | 5 | 383 | |
| | Average | 1 | 1 | 3 | 10 | 23 | 9 | 5 | 8 | 5 | 6 | 3 | 1 | 77 | 4.3 |
| Five-Year Average Monthly Total All Spores | | 42 | 33 | 53 | 168 | 377 | 191 | 122 | 135 | 115 | 149 | 213 | 107 | 1704 | |

TABLE V. GROUPING OF FUNGI OF LOS ANGELES AREA BASED ON SEASONAL ATMOSPHERIC INCIDENCE, MAY, 1940, THROUGH JUNE, 1945

I. Present year 'round without obvious seasonal variation in incidence
1. *Chaetomium*
2. *Monilia*
3. *Mucor*
4. *Penicillium*
5. *Rhizopus*
6. *Scopulariopsis*
7. *Sepedonium*
8. *Stachybotrys*

II. Increased in incidence during rainy season (November-April)
9. *Botrytis*
10. *Phoma:* a peak in March or April which may be fortuitous occurred during the first few years of the survey.
11. *Pullularia*
12. *Rhodotorula*
13. Yeasts

III. Increased in incidence during dry season (May-October)

A. With no obvious peak during any one month but generally most abundant during months indicated
14. *Aspergillus:* June through November
15. *Chaetoconidium:* May through September
16. *Fusarium:* increased summer incidence progressively less noticeable from 1940 onward; subsequent study may prove this a non-seasonal form.
17. *Helminthosporium:* April or May through November
18. *Nigrospora:* June or July through October or November; probably fortuitously it was never isolated during February, March, or April during the entire period of the present survey.

B. With superimposed single peak of incidence
19. Actinomycetes: increased from May through October and at height in July and August,
20. *Cephalosporium:* increased from June or July through October and at height from August into October.
21. Rusts: increased from April through October with peak in May.
22. Smuts: like the preceding, increased from April through October with a peak in May or June.

C. With superimposed double peaks of incidence (not always evident each year)
23. *Alternaria:* the spring peak usually occurs in May, the fall peak in November.
24. *Epicoccum:* the spring peak is generally in May, the fall peak generally in November.
25. *Hormodendrum:* on the basis of the slide counts the spring peak may occur in April, May or June; the fall peak is usually in November.
26. *Macrosporium* (and *Pleospora*), the spring peak may occur in April, May, or June; the fall peak in September, October, or November.
27. *Stemphylium:* The fall peak is usually in November; the spring peak may occur in April or May (and in two different years high counts were obtained in January).

the other three organisms are unduly influenced by unusually large counts for *Helminthosporium* in May of 1941, and for the rusts and smuts in May of 1941, 1942, and 1943. In fact, the counts for the rusts in this month for each of these three years exceed those obtained for any of the other spores at any time over the five-year period. It is interesting to note, however, that for both rusts and smuts the counts for this month show a progressive decrease each year from a peak in 1941. It would appear from

this that 1941 marked a height of infestation of the grasses with the parasitic rusts and smuts, with subsequent diminution of the infestation taking place either spontaneously or as a result of bringing more vacant land under cultivation during the war years.

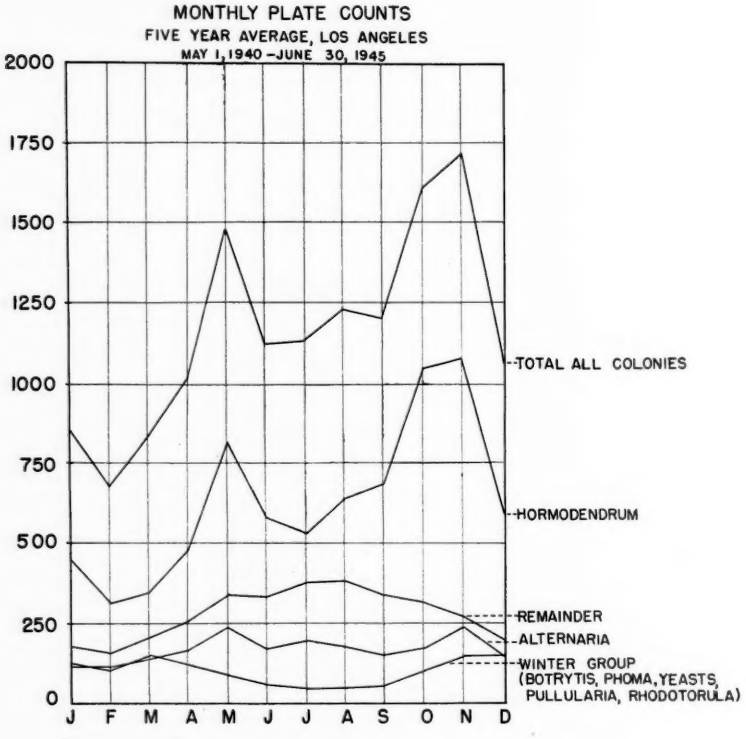


Fig. 2. Monthly plate counts, five-year average.

## DISCUSSION

The average daily maximum temperature here ranges from approximately 65 degrees Fahrenheit in January to 82 degrees in August; the minimum during the same period ranges from 45 to 61. Freezing temperatures are uncommon and transient. Rain is confined to the late autumn, winter, and early spring months, reaching an average annual total of only 15 inches. It is difficult to escape the feeling that the definite seasonal variations in incidence exhibited by the majority of the commonly encountered fungi here are influenced by the regular annual cycles of temperature change and precipitation.

Climatic factors may also explain why the seasonal pattern of *Alternaria* and *Hormodendrum* here appears to be different from that which has been

generally reported elsewhere. Plate studies of various investigators throughout the country as summarized by Feinberg[5] seem to corroborate Morrow's[8] conclusion that in the northern half of this country, the incidence of *Alternaria* and *Hormodendrum* rises from a winter low to

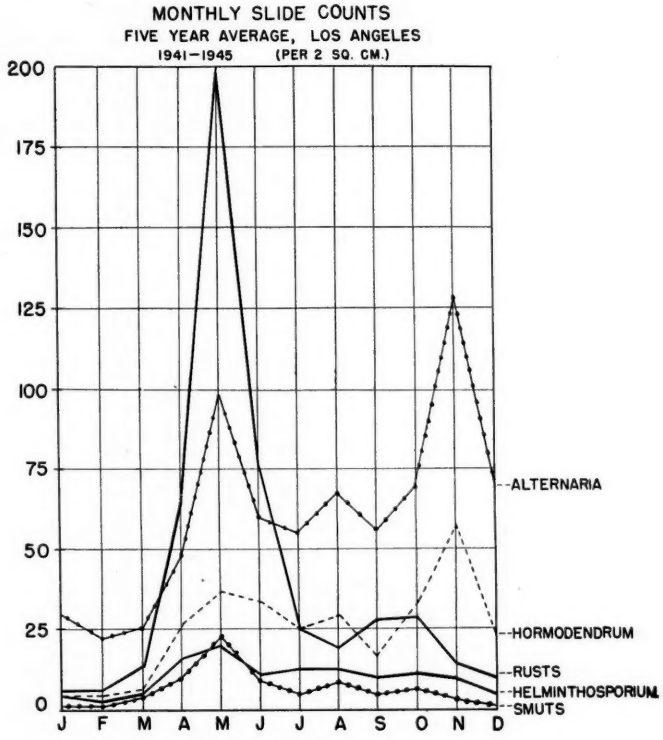


Fig. 3. Monthly slide counts, five-year average.

maxima in the summer. An increased incidence during summer as contrasted with winter takes place here also, but engrafted on the warm weather increase occur noticeable peaks in spring and fall. While the peaks are not invariably present, nevertheless the regularity with which they recur during the five-year period stamps them as forming a definite pattern of incidence in the Los Angeles area, and differentiates these peaks from the sudden marked fluctuations that may occur in the midwest at any time of the year due to sudden changes in weather conditions.

Isolated reports indicate that dual peaks may at times occur east of the Rockies also. This was first pointed out by Underwood[11] from Lincoln, Nebraska, as regards *Alternaria,* and was later confirmed by Durham[3] for North Platte, Nebraska. Bigg and Sheldon[2] mention that the total colony

counts obtained by them in 1938 in Ann Arbor, Michigan, reached peaks in spring and fall, and examination of their chart shows *Alternaria* to be a factor in both peaks. Harris[7] states that in Elyria, near Cleveland, *Hormodendrum* has dual peaks, one in June and another in October and November.

These reports constitute puzzling discrepancies in the prevalent conception regarding seasonal incidence of *Alternaria* and *Hormodendrum* in the northern areas east of the Rockies. Further studies in this zone would appear to be called for to reveal the circumstances under which dual peaks may occur. It is of course possible that the factors producing dual peaks east of the Rockies may have no relation to the factors producing such duality here. Our present feeling regarding the situation here, as stated above, is that both temperature and precipitation are of primary importance in governing spore formation; and that in the case of the two genera under discussion, twin peaks may take place because optimum combinations of both factors are arrived at in spring and fall coincident with the onset and subsidence of the precipitation cycle. Variations from optimum combinations of temperature and precipitation would account for the occurrence of large, small, or no peaks.

Comparison of our findings with those of Harsh and Allen[6] in nearby San Diego reveals a gratifying degree of similarity. The order of frequency of the various genera as given in our Table II compares well with the order found by them. In their chart 1, a spring peak for *Hormodendrum* and a dual spring and fall peak for *Alternaria* are readily apparent, duplicating the findings here.** It is also interesting to note that of the eight dominant genera appearing at the stations studied by the Association of Allergists for Mycological Investigations as reported by Morrow[9] *(Alternaria, Hormodendrum, Penicillium, Aspergillus, Pullularia, Torula, Fusarium, Trichoderma)* all but *Trichoderma* are amongst the most frequent in occurrence here too.

On the other hand, it is surprising to us that we have encountered the actinomycetes with so much greater frequency than has been reported elsewhere. We found them to form 6 to 7 per cent of the total count, ranking next to *Hormodendrum* and *Alternaria* in frequency. In the Chicago area[1] they formed only 1 per cent of the total. Elsewhere[9,12] the reported totals have been even less than this, and in fact in most of the reported surveys[5] they are not even mentioned. This is difficult to understand in view of the widespread distribution of these organisms in the soil. We feel that it is possible that erroneous conclusions have been drawn in some of the surveys. In the first place, unless plates are examined daily, it is certain that many colonies will fail to be detected either before being overgrown or before the colonies have an opportunity to produce sufficient anti-

**What they list as the genus *Sporotrichum* was tentatively identified for them as such by one of us (O. A. P.) at the beginning of their survey; subsequent study of this organism has led to the conclusion that it is actually *Pullularia* and it is so called by us in this paper.

biotic material to protect themselves (as evidenced by the clear zone with which some of the colonies ultimately become ringed). In the second place, even though the plates are examined daily, if dependence is made on gross inspection alone, or in the absence of aid from a trained mycologist as regards microscopic features, it is possible that some of the youngest colonies of actinomycetes may be initially dismissed as being bacterial contaminants only to have them become masked by overgrowth before subsequent inspection of their mature morphology can take place. Attention to these points may lead to revision of present opinion regarding the frequency with which these organisms may be encountered in the air in other parts of the country.

It was noted by us early in this survey that *Hormodendrum* outnumbered *Alternaria* on the plates but was in turn outnumbered on the slides. We concluded that an appreciable number of *Hormodendrum* spores that fall singly are so small as to be overlooked in routine slide counting. Harsh,[6] encountering the same situation, has independently come to the same conclusion.

However, from other areas, as for example Chicago, it has been reported that *Hormodendrum* outnumbers *Alternaria* on both plates[1] and slides.[4] Since some single *Hormodendrum* spores must be overlooked in slide counting in Chicago as well as here, the answer to the different experiences in the two areas must lie primarily in the method of counting the *Hormodendrum* spores.

Durham's[4] slide count figures for the Chicago area are based on counting each individual *Hormodendrum* spore in each clump. We (as does Harsh[6]) count each clump as a single spore. Harsh noted that in San Diego clumps constitute about 20 per cent of the total count and the average number of spores per clump is about 30, so that to obtain an approximation of the total number of individual spores a factor of 7 may be used. Were we to use this factor, our annual slide count total of *Hormodendrum* spores would change from 291 (five-year average) to approximately 2,100, which far exceeds our annual total of *Alternaria* spores (five-year average 726). Conversely, if we divide Durham's reported average seasonal total count for *Hormodendrum* for Chicago (5,726) by 7, the resulting figure (818) becomes less than the *Alternaria* count (3,690) for that area, and the reversal of the ratio of *Hormodendrum* to *Alternaria* as between plates and slides appears in the case of Chicago also. Thus it is simply a mathematical coincidence that it is possible to get a *Hormodendrum* slide count greater or less than the *Alternaria* slide count depending on whether one counts all individual *Hormodendrum* spores regardless of clumping, or merely counts each clump as a single spore.

One cannot state that the one method of counting is inherently more accurate than the other. The method to be used depends on what information one desires to secure. Ideally, it would be best to use both methods simultaneously to yield maximum information.

Durham's[4] method reveals the absolute total number of *Hormodendrum* spores. Our method establishes a more valid parallelism between plate counts and slide counts, since obviously no matter how large a clump may be, it can produce only one colony on a plate, no more than a single spore.

## SUMMARY AND CONCLUSIONS

A survey of the atmospheric incidence of fungus spores in the Los Angeles area was carried out over a period of five years by daily exposure of both plates and slides. Some sixty-odd genera and families were identified, of which twenty-seven were of frequent occurrence.

Of the latter, eight showed no seasonal variation in incidence *(Chaetomium, Monilia, Mucor, Penicillium, Rhizopus, Scopulariopsis, Sepedonium, Stachybotrys)*. The remaining nineteen revealed seasonal fluctuations on the basis of which it was possible to group them as follows: those with generally increased incidence during the rainy season *(Botrytis, Phoma, Pullularia, Rhodotorula,* yeasts); those showing generally increased incidence during the dry or summer season with no specific peaks *(Aspergillus, Chaetoconidium, Fusarium, Helminthosporium, Nigrospora),* with superimposed single peaks (actinomycetes, *Cephalosporium,* rusts, smuts), and with superimposed twin peaks *(Epicoccum, Hormodendrum,* and members of the *Alternaria* tribe consisting of *Alternaria, Macrosporium,* and *Stemphylium)*. That so large a number of organisms show seasonal variations may be due to climatic factors, which also may govern the twin peak pattern of *Epicoccum, Hormodendrum,* and the *Alternaria* tribe.

The predominating organisms on the plates were, in order of frequency, *Hormodendrum, Alternaria,* actinomycetes, *Epicoccum, Pullularia, Penicillium,* yeasts, *Rhodotorula, Macrosporium, Aspergillus, Stemphylium, Helminthosporium,* and *Fusarium.* These constituted about 95 per cent of all colonies. *Hormodendrum* formed about one-half of all colonies, *Alternaria* about one-seventh, the remainder of the predominating group about one-fourth. The average curve of incidence of the total fungus spore population in the air is primarily a function of the additive effects of *Hormodendrum* and *Alternaria:* it begins with a low point in February, then rises gradually to a peak in May; during June and July some recession takes place, though counts still remain high; another rise then takes place to a second (and from the present data, the greater) peak in November; recession then occurs to the winter low.

On the slides, *Alternaria* spores predominated to the extent of averaging about 40 per cent of the total spore count. The reason that *Hormodendrum* counts were less than *Alternaria* counts on the slides, but greater on the plates, must be that a large number of single *Hormodendrum* spores are so tiny as to be overlooked on the slides. The fact that *Hormodendrum* slide counts here are low in comparison to counts reported elsewhere is due to the circumstance that clumps here were counted as single spores whereas

in counts elsewhere each spore in each clump has been counted. It is shown to be a matter of mathematical coincidence that it is possible to obtain *Hormodendrum* counts which exceed or are less than the *Alternaria* slide counts, depending on which method of counting is used.

Though the actinomycetes are widely distributed in the soil and were found by us to be third in order of frequency in the air, most of the atmospheric surveys in the literature of allergy make little or no mention of them. Attention is directed to two possible errors of technique which may play a role in explaining this singular circumstance: first, failure to inspect exposed plates before these slow-growing organisms become overgrown; second, failure to differentiate the very young colonies from bacterial colonies, with overgrowth again occurring before the mature morphology becomes obvious.

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# ALLERGIC EPILEPSY

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THE existence of allergic epilepsy is certain to provoke skepticism among many of you. We, too, shared this skepticism until our studies of the electroencephalograms of allergic children impressed us with the resemblance between many of these records to those of some children with convulsive disorders. In the children with allergy, as well as in those who had convulsive disorders in addition to allergy, we found a high incidence of one abnormality, occipital dysrhythmia.[7] We present here our observations on thirty-seven children under fourteen years of age with convulsive disorders of grand and petit mal type who also have evidence of allergy, whom we have studied for allergy and electroencephalographically.*

TABLE I. CLASSIFICATION OF TYPES OF ELECTROENCEPHALOGRAMS

| |
|---|
| 1. Regular Rhythmic-Repetitive Electro-Activity, Stable to Overventilation. |
| 2. "Within Normal Limits," Stable to Overventilation. |
| 3. "Within Normal Limits," Unstable to Overventilation. |
| 4. Irregular, No Further Changes to Overventilation. |
| 5. Irregular, With Further Changes to Overventilation. |
| 6. Dysrhythmia, Predominantly Frontal. |
| 7. Dysrhythmia, Predominantly Occipital. |
| 8. Spike-and-Waves. |
| 9. Focal Disturbance. |

## CLASSIFICATION OF ELECTROENCEPHALOGRAMS

The classification of electroencephalograms used in this study by one of us (H. L.) is shown in Table I. Groups 1, 2 and 3 are considered to be within normal limits for children. The remainder increase in degree of abnormality. A normal electroencephalogram is illustrated in Figure 1. One within normal limits in a child with rhinitis, asthma, and eczema but without convulsions is shown in Figure 2. Occipital dysrhythmia is illustrated in Figure 3 by the record of an eight-year-old girl with eczema who had no convulsive disorder. This type of tracing was found in 45 per cent of sixty-three allergic children which we have previously reported.[7] Occipital dysrhythmia in patients with neurodermatitis has

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Presented before the Seventh Annual Congress of The American College of Allergists, February 11-14, 1951, Chicago, Illinois.
Approved for publication April 25, 1951.
*A six-channel Grass electroencephalograph was used, six monopolar or six dipolar tracings being recorded simultaneously for about twenty minutes. No sleep records were used in this study.

been reported by Sternberg and Baldridge.[18] A similar record in a boy with allergic encephalopathy is included in Jasper's article on electroencephalography in children.[10] In a study of eighty allergic children with convulsions by Chobot et al,[1] abnormal electroencephalograms were found

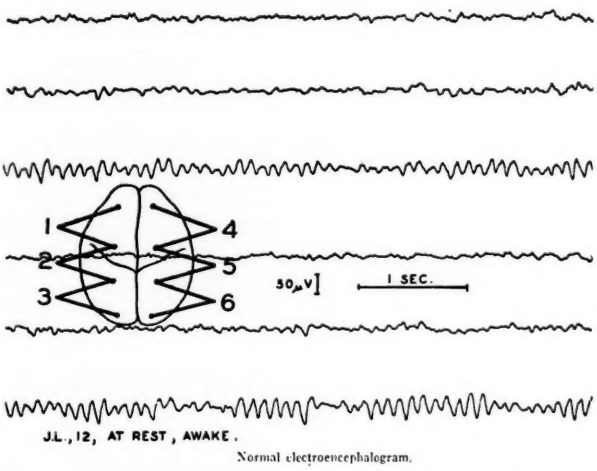


Fig. 1. Normal electroencephalogram in a twelve-year-old child.

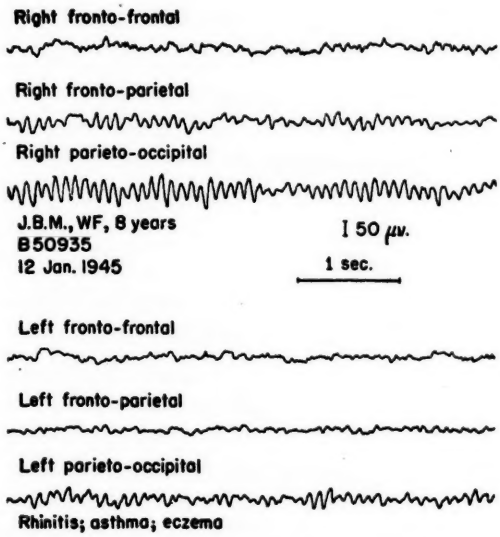


Fig. 2. Electroencephalogram within normal limits in an eight-year-old allergic child.

in 33 per cent of the patients and in 38 per cent of relatives of these allergic children. Occipital dysrhythmia is quite different from the typical slow spike and wave of petit mal (Fig. 4) or the high voltage fast waves of grand mal (Fig. 5).

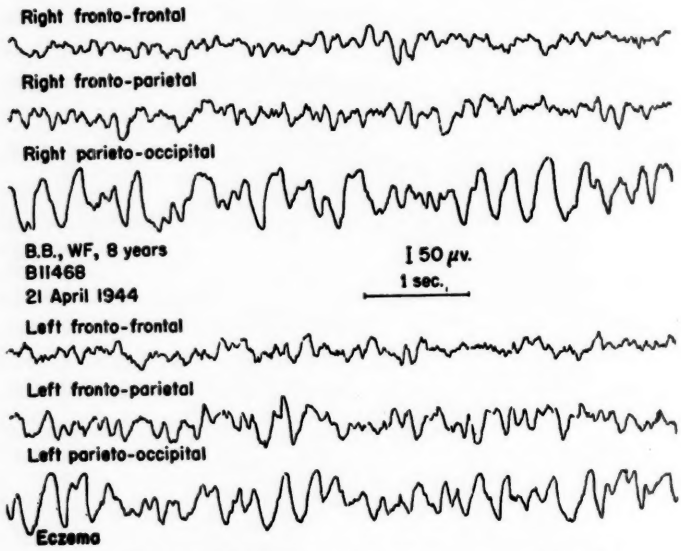


Fig. 3. Electroencephalogram of an eight-year-old child with eczema, howing occipital dysrhythmia.

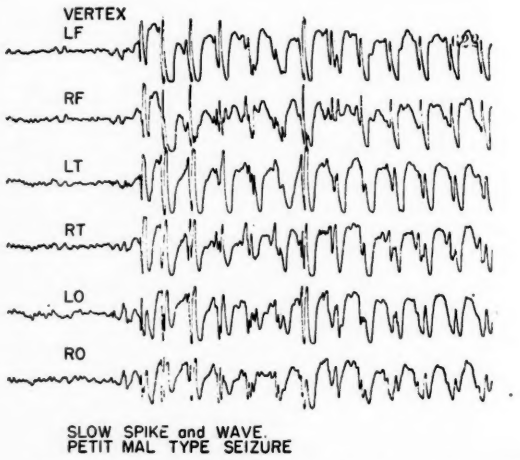


Fig. 4. Electroencephalogram with slow spike and wave of petit mal seizure.

### CRITERIA FOR ALLERGIC EPILEPSY

Our criteria for selection of patients are those of Forman,[8] with the further requirement that no organic brain disease be demonstrable. The patients have been followed from one to eight years with allergic and

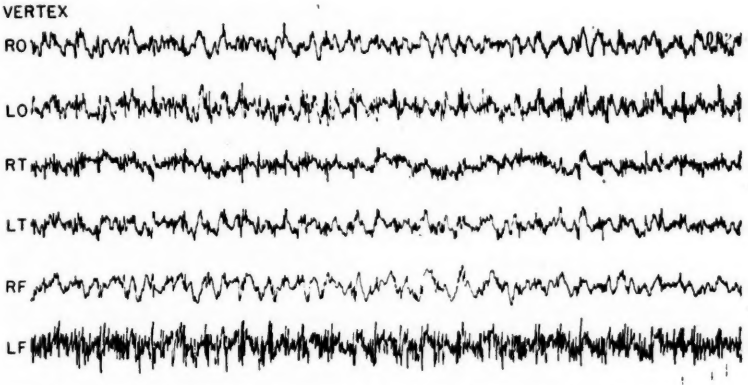


Fig. 5. High voltage fast waves of grand mal seizure.

TABLE II. CRITERIA FOR ALLERGIC EPILEPSY, MODIFIED FROM FORMAN, J.[8]

| |
|---|
| **1. Familial history of allergy.** |
| **2. Personal history of allergy.** |
| **3. Eosinophilia in the blood.** |
| **4. Positive skin tests for protein sensitization.** |
| **5. No organic disease of central nervous system.** |

electroencephalographic studies. The thirty-seven children with convulsive disorders can be separated into two groups, consisting of twenty-two patients with clinical allergy, and fifteen patients without frank allergy but with various features suggestive of or compatible with allergy.

### DIAGNOSTIC FEATURES OF PATIENTS WITH SUSPECTED ALLERGIC EPILEPSY

A comparison of the diagnostic features of the two groups of allergic children shows that both fulfill most of the criteria for allergic epilepsy. A family history of allergy is present in nearly all patients. The personal history is compatible with subclinical allergy in five of the children without frank allergy. Among the allergic group there is a high incidence of asthma, eczema, and rhinitis. It is not surprising to see multiple skin sensitivity in the allergic group, nor to find skin sensitivity to foods in those possibly allergic. It is surprising to find nearly one-half

TABLE III. DIAGNOSTIC FEATURES OF THIRTY-SEVEN CHILDREN WITH SUSPECTED ALLERGIC EPILEPSY

| 22 Clinically Allergic Children | | 15 Clinically Nonallergic Children | |
|---|---|---|---|
| **Family History Allergy** | | **Family History Allergy** | |
| Positive | 19 | Positive | 13 |
| Negative | 3 | Negative | 2 |
| **Personal History Allergy *** | | **Personal History Allergy *** | |
| Asthma | 13 | Wheezy Colds | 2 |
| Eczema | 10 | Convulsions after certain foods | 2 |
| Allergic Rhinitis | 10 | Dislikes and refuses milk | 1 |
| Urticaria | 2 | Convulsions during skin tests | 1 |
| Migraine | 2 | | |
| G. I. Allergy | 1 | | |
| **Skin Tests - Positive to:** | | **Skin Tests - Positive To:** | |
| Airborne Allergens | 19 | Airborne Allergens | 7 |
| Food Allergens | 20 | Food Allergens | 13 |
| Bacterial or Fungus Allergens | 8 | Bacterial or Fungus Allergens | 0 |
| Negative | 1 | Negative | 1 |
| Eosinophilia | 22 | Eosinophilia | 8 |
| Organic Brain Disease | 0 | Organic Brain Disease | 0 |
| Skull films negative | 22 | Skull films negative | 15 |
| Blood Calcium, Sugar Normal | 22 | Blood Calcium, Sugar Normal | 15 |
| Pneumoencephalogram Normal | 1 | | |
| EEG * | | EEG * | |
| Normal range | 1 | Entirely normal | 4 |
| Unstable to Hyperventilation | 1 | | |
| Irregular with change to Hyperventilation | 2 | | |
| Frontal dysrhythmia | 3 | Frontal dysrhythmia | 4** |
| Occipital dysrhythmia | 15 | Occipital dysrhythmia | 11 |
| Spike and Wave | 5** | Spike and Wave | 2** |
| Focal changes | 1** | | |
| **Combined with occipital dysrhythmia | | **Combined with occipital dysrhythmia | |

*Total exceeds 37 because of multiple allergies and EEG abnormalities present in certain patients.

of the so-called nonallergic children reacting to air-borne allergens such as pollens and dusts. Eosinophilia, while not a completely reliable laboratory criterion for allergy, was present at some time in all the allergic children and in one-half of the nonallergic. Stool specimens were negative for parasites in all patients before we considered eosinophilia suggestive of allergy. As nearly as could be ascertained, no organic brain disease was present in any patient, and all had negative serological tests for syphilis.

The electroencephalograms showed occipital dysrhythmia in fifteen of twenty-two allergic children. This abnormality was combined with spike and wave pattern in five patients; one child also had focal changes. Among the fifteen children without clinical allergy four had normal records; occipital dysrhythmia was present in eleven, combined with frontal dysrhythmia in four and spike wave pattern in two.

ELECTROENCEPHALOGRAPHIC FINDINGS

In the children we are reporting, a graphic presentation of the incidence of the types of electroencephalogram encountered shows that the spike and wave, and high voltage fast wave pattern were infrequent find-

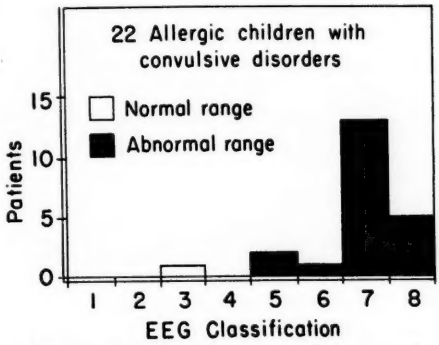


Fig. 6. Types of electroencephalograms in twenty-two allergic children with convulsive disorders.

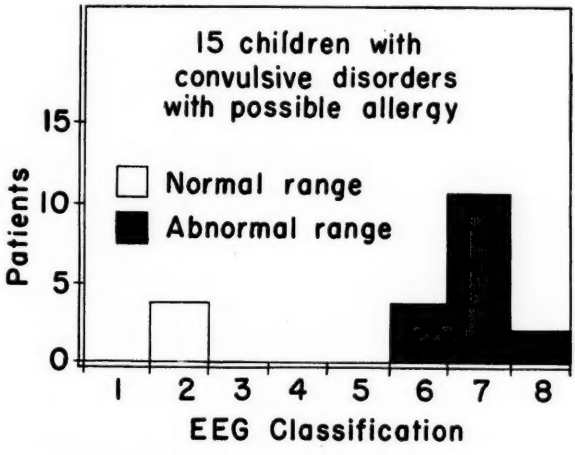


Fig. 7. Types of electroencephalograms in fifteen children without clinical allergy with convulsive disorders.

ings in spite of clinical petit or grand mal convulsive disorder in all of the patients. In contrast to this expected abnormality, we find that occipital dysrhythmia without any other abnormality was the most frequent pattern in the thirty-seven children we have studied. It was present in twenty-seven (73 per cent) of the thirty-seven children. It is noteworthy that this same percentage, namely, 73 per cent, of occipital dysrhythmia

was present in the twenty-two clinically allergic children and in the fifteen children without frank allergy (Figs. 6 and 7).

## ILLUSTRATIVE CASES

The clinical histories of four allergic children are presented to illustrate the relationship of the allergic to the convulsive disorder.

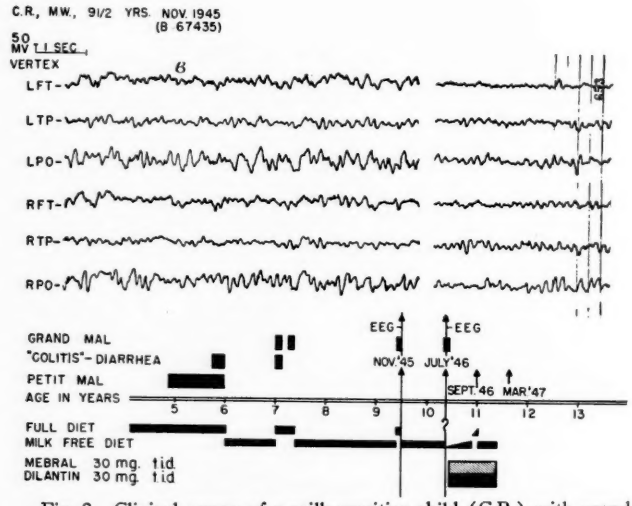


Fig. 8. Clinical course of a milk-sensitive child (C.R.) with grand mal seizures.

K. K., a white girl, was first seen on May 22, 1942, at the age of nine years. For two years she had had innumerable daily petit mal attacks, which were not reduced in frequency by 150 mg of phenobarbital daily. Dilantin sodium, 0.1 gm, in addition was then used without change in symptoms. Phenobarbital was discontinued, and dilantin sodium, 0.3 gm daily, decreased the episodes to twenty to fifty a day but failed to improve them further in a three-month trial period which immediately preceded hospital admission for study. Her past history revealed that she had had severe gastrointestinal symptoms in early infancy from cow's milk. At eight months of age, when breast milk was discontinued temporarily, she had urticaria from cow's milk. Perennial asthma was present from fifteen months to nine years of age. Since the age of one year she had taken a general diet containing up to one quart of milk daily. During her hospital stay, at nine years of age, direct intradermal skin tests and passive transfer tests showed strongly positive (+++ to ++++) reactions to milk, beef, dust, and grasses. X-rays of the skull were negative, blood sugar and glucose tolerance tests were normal, blood calcium was 10.3 mg per cent. Her I.Q. was 134. The initial electroencephalogram showed paroxysmal generalized and occipital dysrhythmia. Treatment consisting of an elimination diet, supplementary calcium and oral vitamin B complex was started upon completion of these studies. From this time until the present, nearly nine years, she has had no seizures and no asthma, and has needed and received no anticonvulsant medication. During the past nine years she

has had thirteen electroencephalograms. Within six months after starting the elimination diet the electroencephalographic tracings became more stable to overventilation, and within two years the electroactivity became and has remained entirely within normal limits. The patient has refused to resume a milk-con-

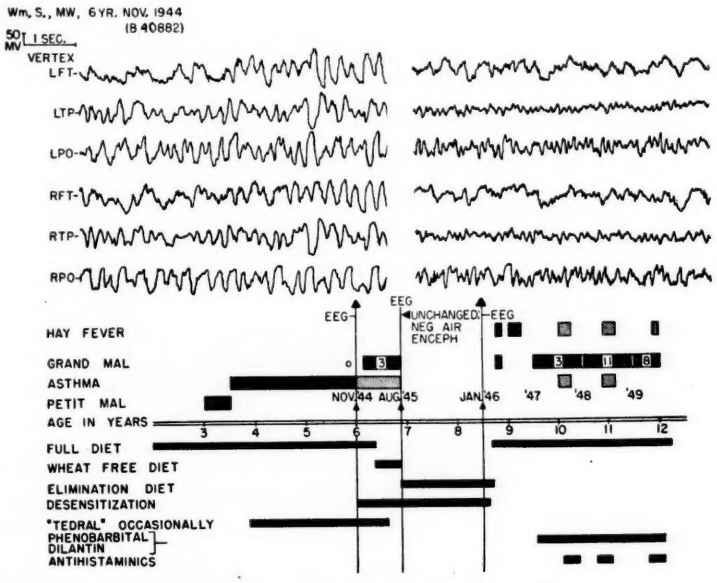


Fig. 9. Clinical course of a pollen- and food-sensitive child (Wm. S.) with petit and grand mal seizures. Improved on allergy regimen, with relapse after it was discontinued.

taining diet since less than one-half ounce of milk tried on two occasions after two years of avoidance produced vomiting, urticaria, and "fainting sensations" within ten minutes. After three years very small amounts of milk in cooked foods were tried briefly with a little coincidental deterioration in the electroencephalogram. On rare occasions, now, if she inadvertently is given food containing any milk, she can detect it at once, and her skin becomes red. At present the patient is eighteen years old, is perfectly well in all respects, and is an honor student and a leader in college. She still continues to use a milk-free diet, with supplementary calcium and vitamins.

The clinical course of another, but less highly milk-sensitive, child with a convulsive disorder illustrates several relapses on abandoning a diet (Fig. 8). C. R., a white boy, aged nine and one-half years, was first seen in 1945 with grand mal seizures. Petit mal began just before he was five years old and lasted until six years of age. He developed colitis and diarrhea near the end of his fifth year. A milk-free diet was begun at this time and continued for one year, during which he was perfectly well. At seven years a full diet was resumed, and almost at once diarrhea and grand mal developed. A milk-free diet for nearly two asymptomatic years was followed again by grand mal on returning milk to the diet in 1945. At this time his first electroencephalogram showed occipital dysrhythmia. A second electroencephalogram in 1946, nearly a year after milk had again been elim-

inated, showed definite improvement, with a record within normal limits. In spite of the electroencephalographic improvement, and because the boy had his only convulsion in a year the night before this electroencephalogram, after breaking his diet by eating ice cream, he was started on mebaral and dilantin by the consulting

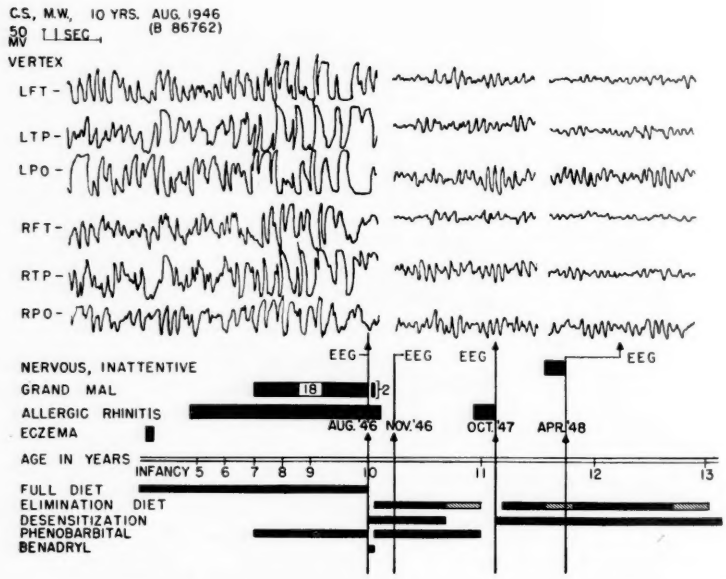


Fig. 10. Clinical course of a pollen- and food-sensitive child (C. S.) with grand mal seizures, whose allergy and convulsive disorder improved and remained controlled on an allergy regimen.

neurologist. He continued with the anticonvulsant and a less restricted diet for the remaining year he was followed and remained clinically well.

A third patient again illustrates simultaneous improvement of allergy and convulsive symptoms on an allergy regimen, with recurrence when these measures were abandoned (Fig. 9). Wm. S., a six-year-old white boy, was first seen in November, 1944. He had had petit mal attacks from three to three and one-half years of age. Perennial asthma began at three and one-half years of age. He had his first generalized convulsion the night before his hospital admission in November, 1944, when he was six years old. The electroencephalogram on the day of admission showed generalized and occipital dysrhythmia. This is illustrated in Figure 9. Intradermal skin tests were positive for pollens, dust, wheat, and corn. Pollen and dust desensitization were started at once, with some decrease in asthma. After several months a wheat-free diet was started, because of three convulsions. In August, 1945, he was admitted to the neurosurgical service for reinvestigation. At this time the electroencephalogram was unchanged, x-ray of the skull and air encephalograms were negative, as was blood chemistry. Hyposensitization was resumed, and a wheat-free and corn-free diet was rigidly followed. A third electroencephalogram five months later, January, 1946, was much more stable. During this period he had had no convulsions or asthma and no symptomatic medication. The parents discontinued both diet and hyposensitization in March, 1946, because

TABLE V. RESULTS OF COMBINED ANTIALLERGIC AND DRUG THERAPY IN THIRTY-SEVEN CHILDREN WITH ALLERGY OR SUSPECTED ALLERGY

| | Patients with Convulsions | | Number Patients Improved | Patients Requiring Sedation | |
|---|---|---|---|---|---|
| | Before Allergy Rx | After Allergy Rx | | Before Allergy Rx | After Allergy Rx |
| Pts. with Clinical Allergy | 22 | 4 | 18 | 20 | 9 |
| Pts. with no Clinical Allergy | 15 | 9 | 6 | 15 | 14 |
| Total | 37 | 13 | 24 | 35 | 23 |

the boy was so well they considered him "cured." Within two weeks after a general diet was resumed and desensitization was discontinued, convulsions recurred and hay fever began. He had nineteen major grand mal convulsions in the next two and one-half years in spite of continuous daily medication with phenobarbital and dilantin. Hay fever and asthma were fairly well controlled with antihistamines. Since the hopeful parents have been told by several physicians and believe that both allergy and convulsions will be outgrown at puberty, they are awaiting this fortunate state in preference to resuming antiallergic measures.

C. S., a white boy, aged ten years, was discovered quite by accident to have hay fever, since this was not mentioned in the presenting complaint, so concerned were the parents over grand mal seizures which had been present for three years uncontrolled by phenobarbital. He, too, discontinued an elimination diet and desensitization after one year because of good health. The convulsions did not recur, although his behavior and school work deteriorated at this time due to excessive nervousness and inattention. Hay fever recurred two months after desensitization was stopped. Both elimination diet and injections were resumed and continued for two years. At present, treatment consists only of desensitization. He has had no hay fever for three years, no convulsions for four years. He receives no medication for either hay fever or convulsions. His last electroencephalograms of September, 1949, are much improved. A report in December, 1950, states that he continues to be asymptomatic.

It is our opinion that the clinical course in these four children shows close correlation between their allergic state and their convulsive disorder. In addition, we consider that the electroencephalographic changes may be interpreted as an objective confirmation of the clinical findings.

### TREATMENT IN CHILDREN WITH CONVULSIVE DISORDERS

Treatment in the thirty-seven children has consisted of antiallergic measures: i.e., desensitization, elimination diets, and precautions against environmental allergens. In addition, drug therapy for allergic symptoms and anticonvulsants have been used as indicated. Sedatives were never deliberately discontinued until patients had been asymptomatic for a period longer than their longest previous remission. Convulsions were controlled in twenty-four of thirty-seven children with this combined treat-

TABLE VI. TREATMENT AND RESULTS IN ALLERGIC PATIENTS

| No. | Patient | Previous Sedative | Final Drug Rx | | Allergic Treatment | | Allergy Controlled | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | Sedative | A* | Diet | Desens. | Complete | Partial | Unchanged |
| | | | Eighteen Children with Convulsions Controlled | | | | | | |
| 1 | C. C. | P | — | — | + | — | + | — | — |
| 2 | C. R. | P | — | — | + | — | + | — | — |
| 3 | K. K. | P-D | — | — | + | — | + | — | — |
| 4 | C. S. | P | — | — | + | + | + | — | — |
| 5 | W. S. | P-D | — | — | + | + | + | — | — |
| 6 | T. B. | — | — | + | + | + | + | — | — |
| 7 | J. G. | — | — | + | + | + | + | — | — |
| 8 | J. Sn | T | — | + | + | + | + | — | — |
| 9 | M. R. | P-D | P-D | + | + | + | — | + | — |
| 10 | J. St. | P | T | — | — | + | — | + | — |
| 11 | M. Vic. | P | — | + | + | + | — | + | — |
| 12 | L. W. | D | D | — | + | + | — | + | — |
| 13 | J. H. | P | — | + | + | + | — | + | — |
| 14 | C. A. | D | + | — | + | — | — | + | — |
| 15 | L. B. | P | P | — | + | — | — | + | — |
| 16 | G. H. | P | — | — | + | — | — | + | — |
| 17 | F. J. | D | — | — | + | — | — | — | + |
| 18 | M. Ver. | P | — | + | + | + | — | — | + |
| | | | Four Children with Convulsions Unchanged | | | | | | |
| 19 | J. C. | P | P-D | + | — | + | — | + | — |
| 20 | J. T. | D | D | — | + | + | — | + | — |
| 21 | P. S. | D-T | P | — | + | — | — | — | + |
| 22 | C. O. | P-D | P-D | — | — | — | — | — | + |

*A—Allergic drugs P—Phenobarbital D—Dilantin-sodium T—Tridione

ment. Eighteen of the twenty-two allergic children and six of those without clinical allergy comprise the children with good therapeutic results, as shown in Table IV. Twenty of the twenty-two allergic children had had sedatives before starting an allergy regimen; nine required sedation while on or after discontinuing antiallergic measures. In many of these patients sedatives were combined with antispasmodic drugs primarily used for asthma, but they, too, are included among those still requiring sedation. Fourteen of the fifteen children without frank allergy still required sedation for control of convulsions. The antiallergic regimen may have contributed to improvement in the six children of this group who improved, although control of convulsions was not effected as rapidly as in the clinically allergic group.

Allergic symptoms—hay fever, asthma, eczema—were controlled completely in eight and partially in ten of the allergic children. In two whose allergy was partially controlled convulsions were unimproved. A summary of the treatment and results in the twenty-two allergic children are shown in Table V.

## DISCUSSION

It is difficult to evaluate any therapeutic measure used in the treatment of chronic disease, since it is almost impossible to have exactly comparable untreated controls. This is particularly true when one is considering the results of treatment in children with allergy and epilepsy, each condition of varying duration and severity, characterized by capriciousness and affected by many nonspecific factors, for whom no uniform treatment can be ordered. For these reasons we do not feel justified in

making any sweeping conclusions regarding results of treatment in these patients. The present study was not primarily designed to test the value of any therapy, but rather to survey the clinical findings to determine whether the allergic factors present could be of possible importance. We consider the over-all clinical results after antiallergic treatment in this group of thirty-seven children with convulsive disorders as highly suggestive, but not conclusive, evidence that improvement of the allergy was related to the improvement in the convulsive disorder, which occurred in twenty-four children.

We do not wish to leave the impression that we believe that all—or even much—epilepsy is on an allergic basis. On the contrary, such cases are few and far between, in spite of a growing literature on the subject.[2,3,5,6,9,11,13,15,16, 17,19,20,21] Nevertheless, there are children with convulsions and allergy whose electroencephalograms do not show the accepted spike and wave or fast wave pattern thought to be characteristic of idiopathic convulsive disorders but rather an entirely different pattern, occipital dysrhythmia, which we have found in uncomplicated allergy. Such children, having failed to respond satisfactorily to anticonvulsant drugs alone, are often further benefited by control, or at least improvement of their allergic disorder. This may mean simply a response to improved general health, or it may signify a similar origin of the two complaints. The similarity between the electroencephalograms of allergic children with or without convulsions suggests that allergic reactions may affect the central nervous system in certain allergic individuals, and that clinical convulsions may be merely the expression of an exceeded threshold in such patients. The fundamental mechanism for the production of convulsions is still incompletely understood, although innumerable studies of this problem have been and are being made and various theoretical explanations have been offered.[4,12,14] If the recognition of allergy as a contributing factor will be the means of removing even a few patients from the group of idiopathic epilepsy and thereby reducing it even a small fraction, the concept of allergic epilepsy will be worth while.

## SUMMARY AND CONCLUSIONS

1. Thirty-seven children with convulsive disorders, who also had evidence of allergy, had both allergic and electroencephalographic studies.

2. The patients had several of the following: a family or personal history of allergy, eosinophilia, positive skin tests, and no demonsfrable organic brain disease. Patients were under observation from one to eight years.

3. Twenty-two patients had clinical allergy. Fifteen had no frank personal allergy.

4. Occipital dysrhythmia was present in the electroencephalograms in twenty-seven children (73 per cent) of the entire series.

5. Four case reports are presented in which control of allergy was accompanied by clinical and electroencephalographic improvement. Discontinuing the allergy regimen was accompanied by recurrence of convulsions and allergic symptoms.

6. The convulsive disorder was controlled in twenty-four patients on combined antiallergic and symptomatic treatment. Eighteen of these were allergic children, and six were without frank allergy.

7. Allergic symptoms were controlled completely in eight and partially in ten of the allergic children.

8. We conclude that children with convulsive disorders who also have evidence of allergy merit trial of antiallergic measures in addition to and in conjunction with anticonvulsant therapy.

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# THE USE OF ACTH IN THE TREATMENT OF AMBULATORY ASTHMATIC PATIENTS

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A CRITICAL evaluation of the laboratory studies done on forty patients given adrenocorticotropic hormone therapy shows that, from a clinical point of view, and especially in older people, such studies are practically useless in determining the amounts needed or the time interval between injections. The treatment and clinical courses of eleven of the patients who had been previously hospitalized and given the usual studies in no way differed from those treated ambulatorily.

There is an undoubted close relationship between the drop in eosinophil cells and the patient's symptomatic relief following ACTH therapy. There are some patients, however, who respond well but in whom no great eosinopenia is noticeable and others, chiefly nonasthmatic, in whom there is little therapeutic result, although eosinopenia occurs. In other fields of medicine this may be important, as in the case of a patient who might conceivably suffer from both rheumatoid arthritis and Addison's disease. In allergic conditions, and especially bronchial asthma, allergic or nonallergic in origin, clinical results have been almost immediate and obvious. If the patient does not react favorably to the dose given, the amount can always be increased. In almost all cases, the cellular response only corroborates what is clinically apparent. Laboratory studies, usually from several hours to several days old, and always expensive for the patient, have done little to determine the patient's present dosage or interval.

One by one the various laboratory tests for cortical function were discontinued until we sought our contraindications for treatment initially by history and subsequently by physical examinations and occasional urinalyses and vital capacity determinations. In ambulatory patients, we do not like to use ACTH in the presence of marked hypertension, nephritis, cardiac lesions or low cardiac reserve, active or moderate but arrested tuberculosis, diabetes, peptic ulcer, furunculosis, or clinical endocrine imbalance. We have, however, used ACTH in patients with heart disease, hypertension, and both moderate and severe diabetes with no untoward effects. The dosage levels necessary to improve bronchial asthma, present alone in thirty patients, and also contact dermatitis and dermatitis medicamentosa in ten others, have shown no immediate marked or deleterious re-

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Expenses defrayed, in part, by The Asthma Research Foundation, Inc., Boston, Massachusetts.

Presented at the Seventh Annual Congress of the American College of Allergists, February 11-14, 1951, Chicago, Illinois. Approved for publication, April 16, 1951.

actions, at least none as incapacitating as the conditions themselves. In the latter group of patients, who presented self-limiting clinical syndromes and who were therefore treated for only short periods of time, no ill effects were seen and would require no consideration.

Incidentally, skin tests when checked were found to be unchanged. It was concluded from this that reagin titers and passive transfer tests would not be affected. When these tests were done, such conclusions were found to be true. In nonemphysematous patients, vital capacity was generally increased during remissions, to return to earlier levels during relapses. From a clinical point of view, the drug was found to control the patient's clinical allergic symptoms and to change nothing else, excepting perhaps in ways not measurable clinically.

Routinely, the patients were placed, as usual, on diets low in sodium chloride with no additional salt and given potassium as the chloride, citrate, or iodide by mouth, in doses of 1.5 to 3 gm daily. Depending upon the severity of the patient's condition, the schedule of treatment began with two, three, or four injections daily for as long as it took to achieve relief. The dose (using Wilson's ACTH) was 20 mg every six hours or every eight hours, usually for two or three days. For the Armour preparation, which is between one-half to one-third as potent, the doses varied from 25 to 50 mg each injection. In each case, individualization was necessary, depending not only on the severity of the condition but on the presence of other limiting factors. On schedules of this type, the patient is given his injections at the hospital or office for the first days of treatment, taking two or three injections each day and taking the subsequent injections at home. There was no difficulty because almost all of the asthmatic patients were experienced in injecting epinephrine.

If, on whatever schedule was chosen, the patient did not show great improvement after forty-eight hours, the dose was increased by 5 or 10 mg on the same interval schedule. One patient in forty received 40 mg every eight hours (Wilson), but no other patient has required such a great dosage. As soon as improvement was apparent, the dose remained the same, but the injections were taken at wider intervals, being changed from six-hourly to eight-hourly, or from eight-hourly to twelve-hourly. This latter schedule calls for an injection, at say 10:00 a.m. and 10:00 p.m., the patient taking the evening injection at home. If improvement was maintained, the dose was usually but not always increased by approximately 50 per cent and the schedule changed to one injection each day.

For example, a patient who was well on 20 mg every eight hours went to 30 mg every twelve hours. With continued improvement on this schedule, the dosage was changed to 40 mg once daily, and in the absence of symptoms, the dose was dropped by 5 mg every other day to the 10 or 15 mg once daily dosage level. Thereafter, we have tried to diminish the dose by 2 mg each time. Our minimum dose has been 10 to 12 mg every forty-

eight hours. One patient reduced her injection level to 6 mg every forty-eight hours, but relapsed and had to increase the dose to 12 mg every two days.

Successive days can, on this schedule then, be represented by doses of 35, 30, 25, 20 and 16 mg. If the patient wheezes, either the dose is increased or the injections are made more frequent. When the patient continues to stay well, injections of 16 or 20 mg are given at intervals, first of one and two days, and then, if possible, at fifty-six or sixty hours. At the first sign of relapse, the dose is, of course, increased. The patients have either gone into complete remission, maintained for some weeks or months, or have required continued ACTH treatment, at intervals no greater than forty-eight to fifty-six hours.

Once weekly the patient is examined for edema. The heart and blood pressures are checked and a urinalysis is usually done. If normal, after several weeks of treatment, these are omitted. Two patients have shown a glycosuria with green reactions, and six, an ankle edema which disappeared with lower dosage or diet control. The patients for whom such treatment was initiated in the hospital remained for three to fourteen days and then continued with office visits as frequently as was necessary.

Usually the patients purchased their own material and took injections at the interval which had been discovered would keep them free of symptoms. By this means, the patient took the minimum amount of ACTH at the widest possible interval with the least trouble to himself, his family, and his physician and at the smallest possible expense. As is common with all treatment of this type, the amounts needed and the injection intervals had to be individualized, but our experience shows that such individualization is within the limits of two injections daily to one in two days. No one has needed more and none of our actively treated patients are taking less, although we continuously try to widen the interval for these patients, with, however, little or no success. During periods of stress or intercurrent infection, the dose may temporarily have to be adjusted upwards.

In the ten patients with self-limiting conditions, such as contact dermatitis and drug rashes, injections every six hours or every eight hours have been given for one week, the patient being hospitalized and under observation daily. The dose is tapered off as soon as the skin is clear, and again the injections are reduced, first in number from four to three and then to two and then to one daily. The doses are then reduced by 5 mg each day, and as soon as the patient has been clear for three or four days, no further treatment is given. In some of these patients, antihistaminic unguents (more effective because of their excellent base rather than for their antihistaminic content) and antihistaminic preparations by mouth have been necessary during the initial days of treatment.

Another untoward reaction must be mentioned: namely, "lumps" at the site of the injection in unskilled patients first giving themselves treatment.

All of the patients have shown a measure of euphoria and the usual increase in appetite and weight, at least during the initial days of ACTH therapy. This soon disappears on maintenance dosage, the patients maintaining their weight but showing normal appetites and no euphoria. One patient seen in consultation showed psychotic changes which were present one week after ACTH therapy was discontinued, at which time relapse occurred although the patient was clear of symptoms while undergoing treatment. Some of the patients have been forced to cease using ACTH therapy because of the expense involved. In all cases to our knowledge, excepting in self-limiting conditions, relapse occurred within a few days to two weeks in those patients continuously exposed to the causative allergens, or in those in whom sinus or bronchial infection was the initial precipitating or a secondary aggravating factor. In those in whom the symptom-free period was used as an opportunity to eliminate allergens or give immunity by injection treatment, the remission was long-lasting. We could not, at any time, state with any certainty that remissions were directly due to the drug itself, alone, or that the length of remission showed any relationship to the dosage given or the duration of treatment.

Four cases will be used to illustrate the typical course of patients taking ACTH therapy. All of these were over forty with asthma of more than ten years' duration. None had responded well to previous treatments.

*Case 1.*—Miss E. B., aged fifty-three, suffered from a history of bronchial asthma lasting over ten years. She had first presented a ragweed hay fever, and then, some weeks following a lobar pneumonia, began to wheeze perennially. She suffers from a chronic sinus infection. Climatic change during the pollen season relieved her nasal symptoms. She wheezes perennially with some amelioration but with no complete freedom while in warm, dry areas. The symptoms were controlled by ephedrine and the usual drugs taken in moderate quantities. She presents no physical abnormalities, excepting for the chronic sinus infection and a mild emphysema with a consistent eosinophilia of approximately 20 per cent. Skin tests show her sensitive to grass and ragweed pollens and to house dust. Intermittent injection treatment has been given her with partial success for five years. Diets, here and elsewhere, have proven the absence of food allergy. On October 2, 1950, ACTH therapy was started with injections three times daily, 16 mg (Wilson) ACTH. The patient's symptoms cleared completely in five days, following which injections of 20 mg were given twice daily. She remained well for three more days, and the dose was reduced to 20 mg once daily. The patient remained completely free of symptoms for approximately ten days. At the end of the same month she came down with a cold and increased the dose to 30 mg twice daily, with no relief. Terramycin was prescribed at the same time in doses of 500 and then 250 mg every six hours. Thereafter, the patient only partially responded to treatment, although she did without ACTH for one week and then began with doses as high as 20 to 26 mg (Wilson) twice daily. Although she had been comparatively free from wheezing during this period, and better than she had been during any other remission during the past ten years, she did not wish to continue and has therefore resumed her oral symptomatic treatment with the usual antispasmodic drugs, which she needed in small quantities while taking the second course of ACTH injections. She states that they are certainly more convenient and less expensive, with relief as complete as that due to ACTH.

*Case 2.*—One of the best results was achieved with a patient, Miss H. L., aged forty-four, with bronchial asthma present for seventeen years, with remissions occurring for two or three months when the condition first occurred, but with no remission of more than one day or two since February, 1947. The condition is perennial, with exacerbations from August through October and with exposure to dust or molds. The usual physical examination and laboratory studies showed no abnormality to be present, excepting for a mild emphysema and hazy sinuses. The skin tests showed large reactions to the animal danders, to the ragweed pollen, and to house dust. There were mild reactions to Hormodendrum and to Monilia. Injection treatment with ragweed pollen, house dust, and mold extracts, and also with vaccine given intermittently, gave the patient little relief. Oral medication had been necessary continuously each day from March 10, 1949, until October, 1950, at which time ACTH therapy was initiated. No oral medication for symptomatic relief has been taken for six months (April 1, 1951). The first injections were 20 mg (Wilson) three times daily for two days, following which the wheezing ceased, leaving only a slight cough. With 30 mg twice daily, there was a slight swelling of the ankles, which cleared with a salt-free diet. Treatment was continued with 30 mg once daily from October 20 to November 16, 1950, at which time the dose was decreased to 20 mg daily, and on December 4, 1950, to 12 mg daily. Since that date the patient has taken 12 mg every other day with complete control of all symptoms. With an injection every third day, she presents a cough and wheezing, and to maintain her good progress must therefore remain on a forty-eight-hour schedule.

*Case 3.*—The third representative case history concerns a sixty-two-year-old woman, Mrs. E. C., who had suffered from bronchial asthma associated with severe sinus infection for twenty-one years. Skin tests have always been negative. Diets have been without effect. Climatic change to Arizona for two years caused partial improvement. The patient has required oral medication for symptomatic relief daily from July, 1944, to October, 1950. She was relieved by aminophylline taken by mouth, by rectum, and by injection. Doses of 20 mg (Wilson) ACTH three times daily for five days completely cleared her chest. The dose was then changed to 25 mg twice daily, and after two days, to 20 mg once daily. After several days, the injections were given at intervals of two days, and now stand at the 20 mg level at two to three day intervals. Twice between October 4, 1950, and April 1, 1951, she has caught cold and has required aminophylline, also necessary during times of stress and with prolonged exposure to cold air. On each occasion, two to four injections of 20 mg taken within the same twenty-four hours have helped clear her symptoms. She has now reduced the dose to twelve to sixteen mg every two days, with no recurrence of her wheezing. It must be noted, however, that with emotional upsets, fatigue, and exposure to cold air, the patient presents a moderate wheeze which requires aminophylline, usually by mouth and sometimes by injection.

*Case 4.*—The fourth representative case report concerns a fifty-one-year-old woman, Mrs. H. C., who suffered from a spring hay fever fourteen years ago, for which she then took injection treatment with severe constitutional reactions. She presents marked, clinically proven, tree and grass pollen, mold and dust sensitivities, for which she is now taking injection treatment with only local reactions. There are no physical abnormalities, excepting for the necessity of pelvic repair following parturition some years ago. She has had two previous courses of ACTH (Armour) therapy given elsewhere, with a relapse in each case within seven days following cessation of treatment. She was given the Armour preparation, taking 10 mg twice daily, with a maximum period of remission of three hours, requiring epinephrine by injection one to three times daily. Symptomatic treatment with other drugs was necessary. The patient increased the dosage to 10 mg three times daily, with relief, and then con-

tinued on 10 to 12 mg (Wilson) twice daily, continuing at this level from December 19, 1950, to April 1, 1951, with symptoms which occur only when she goes below the dosage of 10 mg twice daily. On three occasions she has suffered from intercurrent infections, during which periods doses of 24 mg every eight hours have been necessary for three to five days. The dose can be reduced to 10 to 12 mg twice daily following recovery.

The four female patients chosen as representative case reports are all about the same age, with three markedly allergic and one presenting no allergy. All, as noted, presented bronchial asthma of ten or more years' duration. All had been recalcitrant to treatment, specific or nonspecific. All showed immediate marked improvement, which in one was not lasting, minimal injection amounts being given at intervals of twelve hours to two days, keeping the others completely symptom-free. In these four representatives of forty patients, no irreversible untoward reactions were seen. In the others studied, continued treatment has given similar results over a period of approximately ten months. Cessation of ACTH therapy has always been followed by relapse to the original condition. Patients have not responded equally well to second or third courses, although other manifestations of response were evident. In ACTH we have an ideal drug for use in self-limiting allergic conditions and the treatment of status asthmaticus. It does not replace studies, elimination, injections, medication, or psychotherapy. It can be used with apparent safety for some months in the older infectious, or combined infectious and allergic asthmatic group of patients, if injections are given, as noted, at intervals of twelve hours to two days.

The patients with self-limiting conditions remain in remission. In some who have previously had remissions, ACTH treatment may initiate a long symptom-free period, especially if causative allergens are eliminated and injection treatment for inhalants is continued. In the older, chronic asthmatic patients with continuous wheezing, remissions are not long-lasting; but the patient can be maintained on doses of 6 to 10 mg at intervals no greater than forty-eight to fifty-six hours. We do not as yet know the full effects of prolonged treatment with ACTH for long periods of time. Careful follow-up reports at yearly intervals will be necessary before we can truly evaluate the effects of adrenocorticotropic injection therapy.

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## STANDARDIZATION OF DUST EXTRACTS

### III. Precipitin and Collodion Particle Agglutination Experiments
### IV. Rabbit Skin Sensitivity Experiments

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AN attempt was made to develop a method of standardizing dust extracts by serological means. A dust extract (MR) alone and the extract fortified with staphylococcus toxin or with staphylococcus toxoid as an adjuvant were injected intracutaneously into rabbits. Five groups of rabbits were injected as indicated in Table I. Group I (rabbits 5, 7, and 8) received dust extract and toxin, Group II (rabbits 6 and 9) received dust extract and toxoid, Group III (rabbits 3 and 4) received dust extract alone, and Group IV (rabbits 1 and 2) and Group V (rabbits 10 and 11) were control rabbits which received toxin alone and toxoid alone, respectively.

TABLE I. SCHEDULE OF INTRACUTANEOUS INJECTIONS OF RABBITS

| Date of Injection | Rabbits | | | | |
|---|---|---|---|---|---|
| | Group I* 5, 7, 8 | Group II** 6***, 9 | Group III 3, 4 | Group IV 1, 2 | Group V 10, 11 |
| 12/19/47 | 0.1 ml MR and 0.1 ml Stn (1:2) | 0.1 ml MR and 0.1 ml Std (1:2) | 0.1 ml MR | 0.1 ml Stn (1:2) | 0.1 ml Std (1:2) |
| 12/23/47 | 0.1 ml MR and 0.1 ml Stn (1:2) | 0.1 ml MR and 0.1 ml Std (1:2) | 0.1 ml MR | 0.1 ml Stn (1:2) | 0.1 ml Std (1:2) |
| 12/29/47 | 0.1 ml MR and 0.1 ml Stn (1:2) | 0.1 ml MR and 0.1 ml Std (1:2) | 0.1 ml MR | 0.1 ml Stn (1:2) | 0.1 ml Std (1:2) |
| 1/2/48 | 0.1 ml MR and 0.1 ml Stn (und) | 0.1 ml MR and 0.1 ml Std (und) | 0.1 ml MR | 0.1 ml Stn (und) | 0.1 ml Std (und) |
| 1/6/48 | 0.1 ml MR and 0.1 ml Stn (und) | 0.1 ml MR and 0.1 ml Std (und) | 0.1 ml MR | 0.1 ml Stn (und) | 0.1 ml Std (und) |
| 1/9/48 | 0.1 ml MR and 0.1 ml Stn (und) | 0.1 ml MR and 0.1 ml Std (und) | 0.1 ml MR | 0.1 ml Stn (und) | 0.1 ml Std (und) |
| 1/12/48 | 0.15 ml MR and 0.15 ml Stn (und) | 0.15 ml MR and 0.15 ml Std (und) | 0.15 ml MR | 0.15 ml Stn (und) | 0.15 ml Std (und) |

*The toxin and dust extract were mixed together immediately before injection.
**The toxoid and dust extract were mixed together immediately before injection.
***Died of causes unknown, after sixth injection.
MR = Dust extract used.
Stn = Staphylotoxin.
Std = Staphylotoxoid.
und = Undiluted.

With the sera obtained from these animals, precipitin and collodion particle agglutinin (Cavelti, 1947[1]) titrations against the dust extract were made. The results are summarized in Table II. As may be seen from this table, no precipitation occurred with the sera from the two rabbits that

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Approved for publication May 7, 1951.

received the dust extract alone (Group III) nor, of course, with the sera of the control rabbits (Groups IV and V). The sera from the rabbits that received the toxin-fortified dust extract had a titer of 1:40, and the serum from one of the two rabbits that received the toxoid fortified dust extract

TABLE II. COMPARISON OF THE COLLODION AGGLUTINATION AND THE RING TEST PRECIPITIN TITERS OF THE DUST ANTISERA

| Sera from Rabbits in Group | No. of Serum | Ring Test Titer* | Collodion Agglutination Titer** |
|---|---|---|---|
| I | 5 | 1:40 | 1:1280 |
| | 7 | 0 | 1:160 |
| | 8 | 1:40 | 1:320 |
| II | 6*** | | |
| | 9 | 1:80 | 1:1280 |
| III | 3 | 0 | 1:320 |
| | 4 | 0 | 1:640 |
| IV | 1 | 0 | 0 |
| | 2 | 0 | 0 |
| V | 10 | 0 | 0 |
| | 11 | 0 | 0 |

*Dust extract MR used as antigen.
**Collodion particles were sensitized with dust extract MR.
***Died after the sixth injection.
Group I: Received dust sample MR and staphylotoxin.
Group II: Received dust sample MR and staphylotoxoid.
Group III: Received dust sample MR.
Group IV: Received staphylotoxin.
Group V: Received staphylotoxoid.

had a titer of 1:80, the other rabbit in this group having died after the sixth injection. The collodion particle agglutinin titers of the sera from the rabbits that received fortified dust extract were much greater than the precipitin titers, and even the sera from the rabbits that received dust extract alone showed rather strong collodion particle agglutinin titers. The sera from the control rabbits again did not react with the dust extract.

Of the two antisera (5 and 9) that gave the highest collodion particle agglutinin titers with dust extract, one (serum 5) was tested by both the precipitin and collodion particle agglutination tests with six batches of dust extract (four crude, including MR, and two absorbed concentrated) that had been used in a previous experiment (Scherago, Berkowitz, and Reitman, 1950).[2] Skin tests on dust-sensitive patients were also carried out with the six extracts for purposes of comparison. The skin test reactions were evaluated as in the paper by Scherago, Berkowitz, and Reitman (1950).[2] A summary of the results of the precipitin, agglutination, and skin tests is given in Table III. As can be seen from this table, all the crude extracts had the same precipitin titer (1:80), one of the absorbed concentrated extracts (JH) had a titer of 1:10, and the other (RW) none. With the collodion particle agglutination test no reaction was obtained with the absorbed concentrated extracts, whereas all the crude extracts reacted, two with titers of 1:160, one with a titer of 1:320, and one

with a titer of 1:280. The skin reactivity ratings were determined by averaging the reactions obtained with each extract on thirteen dust-sensitive patients. It is apparent that there was no correlation between the skin reactivity ratings and the precipitin titers or the collodion particle agglutinin

TABLE III. COMPARISON OF THE HUMAN SKIN REACTIVITY RATINGS OF THE DUST EXTRACTS WITH THEIR PRECIPITIN AND COLLODION AGGLUTINATION TITERS IN ANTISERUM 5

| Dust Extract | Type of Extract Concentrate | Skin Reactivity Rating | Precipitin Titer | Collodion Agglutination Titer |
|---|---|---|---|---|
| MR | Crude | 2.38 | 1:80 | 1:1280 |
| BB | Crude | 2.53 | 1:80 | 1:320 |
| MS | Crude | 2.30 | 1:80 | 1:160 |
| MH | Crude | 3.07 | 1:80 | 1:160 |
| JH | Absorbed | 1.46 | 1:10 | 0 |
| RW | Absorbed | 1.77 | 0 | 0 |

titers except for the fact that the crude extracts had higher skin reactivity ratings than the absorbed concentrated extracts, and the crude extracts also had higher precipitin titers and collodion particle agglutinin titers than the absorbed concentrated extracts. Nor was there any correlation between the precipitin titers and the collodion particle agglutinin titers except for the fact that reactions with both tests were obtained with the crude extracts but not with the absorbed concentrated extracts (except for the reaction in low dilution, 1:10, with extract JH with the precipitin test).

It would appear, therefore, that there is some correlation between the precipitinability and collodion particle agglutinability of dust extracts by dust extract antiserum and their human skin reactivity, but that this correlation is only a qualitative one. This qualitative correlation might be of some value in culling out newly prepared dust extracts which might not be potent enough to give positive skin reactions in a large majority of dust-sensitive people.

In an attempt to determine the possibility of using rabbit skin sensitivity as a means of evaluating the allergenic potency of dust extracts, the ten surviving rabbits were tested with intracutaneous injections of 0.1 ml amounts of dust extract MR, fifteen days after they had received their seventh injections. Since none of the animals developed cutaneous reactions at the sites of injection even after forty-eight hours, they were given a second series of intracutaneous injections, in the hope of inducing skin sensitivity. Each animal received the same material that it was given in the first series of injections. Table IV shows the schedule of injections. The injections were made on the back on the left side. Immediately after each sensitizing injection a testing dose of 0.1 ml of dust extract MR was injected intracutaneously on the right side of the backs of the rabbits that were being sensitized against this extract to see if the rabbits had become

sensitized. The animals were observed for a period of one hour and again after twenty-four hours. The results are recorded in Table V.

As can be seen from this table, the animals that received toxin-fortified dust extract (5, 7, 8) began to show sensitivity to dust extract MR after

TABLE IV. INJECTION SCHEDULE—SECOND SERIES

| Group | Rabbit No. | Date of Injection | Dust Extract MR in ml | Staphylo-toxin ml | Staphylo-toxoid ml | Dust Extract MR* for Skin Sensitivity Detection |
|---|---|---|---|---|---|---|
| I | 5, 7, 8 | 2/9/48<br>2/13/48<br>2/17/48<br>2/20/48<br>2/25/48<br>3/4/48 | 0.15 | 0.15 | | 0.1 ml |
| II | 9 | 2/9/48<br>2/13/48<br>2/17/48<br>2/20/48<br>2/25/48<br>3/4/48 | 0.15 | | 0.15 | 0.1 ml |
| III | 3, 4 | 2/9/48<br>2/13/48<br>2/17/48<br>2/20/48<br>2/25/48<br>3/4/48 | 0.15 | | | 0.15 ml |
| IV | 1, 2** | 2/9/48<br>2/13/48<br>2/17/48<br>2/20/48<br>2/25/48<br>3/4/48 | | 0.15 | | |
| V | 10, 11 | 2/9/48<br>2/13/48<br>2/17/48<br>2/20/48<br>2/25/48<br>3/4/48 | | | 0.15 | |

*Given immediately after sensitizing injection.
**Died 2/25/48.

the ninth injection. The reactions were of the delayed type (they were observed and recorded at the twenty-four hour reading) and consisted of erythema and induration. The rabbit (9) that received toxoid-fortified dust extract also showed sensitivity after the ninth injection, but the sensitivity could not be detected after the tenth injection; it was detected again after the thirteenth injection. One of the rabbits (3) that received dust extract alone also reacted after the ninth injection but failed to react after the eleventh or any subsequent injection. The other rabbit (4) that received dust extract alone reacted after the eighth injection but also failed to react after the eleventh or any subsequent injection.

The control rabbits (that received toxin alone and toxoid alone) were not tested for sensitivity to dust extract MR for fear that they might become sensitized to this extract with the test injections.

Since skin reactions had been obtained in all the rabbits that had been

TABLE V. SKIN REACTIONS TO DUST EXTRACT MR IN RABBITS DURING SECOND COURSE OF INJECTIONS

| Rabbit No. | Injected with | Skin Reactions to Dust Extract Injected Immediately after Sensitizing Injection No. | | | | | |
|---|---|---|---|---|---|---|---|
| | | 8 | 9 | 10 | 11 | 12 | 13 |
| 5 | T+MR | — | E, 3*, ** I, 10 | E, 10 | I, 10 | — | E, 10 I, 10 |
| 7 | T+MR | — | E, 20 I, 20 | — | E, 10 I, 25 | E, 10 I, 10 | E, 10 |
| 8 | T+MR | — | I, 10 | E, 20 | — | — | E, 10 I, 10 |
| 9 | Tox+MR | — | E, 20 I, 20 | — | — | — | E, 15 I, 15 |
| 3 | MR | — | E, 2 I, 2 | E, 20 | — | — | — |
| 4 | MR | E, 2 I, 2 | I, 25 | E, 20 | — | — | — |

*All figures indicate the diameter of the lesion in millimeters.
**All reactions were observed 24 hours after skin testing.
T = Staphylotoxin.
Tox = Staphylotoxoid.
MR = Dust extract used.
E = Erythema.
I = Induration.
— = No reaction.

sensitized with the dust extract (MR) when they were tested with extract MR, it was of interest to see how some of these rabbits would react to the other five extracts used in this investigation. For this purpose five of the rabbits( 3, 4, 5, 8, and 9), in whose sera the presence of antibodies (collodion particle agglutinins) against dust extracts had been demonstrated, were selected.

Seventy days after the last dust extract immunizing injection, these rabbits were injected intracutaneously with 0.05 ml amounts of varying dilutions (1:10, 1:100, 1:1000, 1:10,000) of dust extracts MR, BB, MS, MH, JH, and RW. The animals were observed for evidence of any skin reactions at the injection sites for a period of one hour and again at the end of twenty-four hours.

A rabbit that had not been previously injected and whose serum gave negative precipitin reactions to dust extract was also injected. Since all the extracts contained glycerine, a control injection of glycerinized saline (50/50 by volume) was given to each animal.

Only rabbit 5 showed any evidence of skin sensitivity to the dust extracts. In this animal the skin reactions appeared within an hour after the injections in contrast to those in the previous experiment* which appeared only after twenty-four hours. Each reaction consisted of a wheal and erythema. The average diameters of the wheals in centimeters (obtained by dividing the sum of the diameters by 2) are recorded in Table VI. As can be seen from this table, extract MR elicited a reaction of 0.5 cm in a dilution of 1:1000, extract BB elicited a reaction of 1.0 cm in a dilution of 1:1000, extract MS elicited a reaction of 0.5 cm in a

dilution of 1:10,000, while extract MH elecited a reaction of 1.2 cm in a dilution of 1:100. Dust extracts JH and RW did not elicit any cutaneous reactions.

When each skin reaction was evaluated by using a code similar to the

TABLE VI. SKIN TEST REACTIONS TO DUST EXTRACTS IN RABBIT NO. 5 SHOWING THE AVERAGE DIAMETER OF THE WHEAL

| Extract | Dilution of Extract | | | |
|---|---|---|---|---|
| | 1:10 | 1:100 | 1:1000 | 1:10000 |
| MR | 1.5* | 1.3 | 0.5 | — |
| BB | 1.5 | 1.4 | 1.0 | — |
| MH | 1.7 | 1.2 | — | — |
| MS | 1.7 | 1.1 | 1.0 | 0.5 |
| JH | — | — | — | — |
| RW | — | — | — | — |

*All figures are in centimeters.

TABLE VII. COMPARISON OF RABBIT SKIN REACTIVITY RATINGS OF DUST EXTRACTS WITH THEIR HUMAN SKIN REACTIVITY RATINGS

| Dust Extract | Type of Extract Concentrate | Rabbit Skin Reactivity Rating | Human Skin Reactivity Rating* |
|---|---|---|---|
| MR | Crude | 3 | 2.38 |
| BB | Crude | 3 | 2.53 |
| MS | Crude | 4 | 2.30 |
| MH | Crude | 2 | 3.07 |
| JH | Absorbed | 0 | 1.46 |
| RW | Absorbed | 0 | 1.77 |

*Average

one that was used for evaluating the human skin reactions obtained with the same extracts, the following ratings of the crude concentrates were obtained: MR, 3; BB, 3; MS, 4; and MH 2. The absorbed concentrates JH and RW, of course, had ratings of 0. For purposes of comparison, the animal skin reactivity ratings of the extracts are listed along with their average human skin reactivity ratings in Table VII.

As can be seen from this table, there is no correlation between the animal skin ratings and the human skin ratings. For instance, extract MS had the highest reactivity (4) of all the extracts in the rabbit, but its reactivity in the human was the lowest (2.30).

## SUMMARY AND CONCLUSIONS

Using rabbits injected with dust extract and with dust extracts fortified with adjuvants such as staphylococcus toxin and staphylococcus toxoid, an attempt has been made to develop a biological method of determining the allergenic potency of such extracts by means of precipitin and collodion

*(Continued on Page 486)*

# REPOSITORY PENICILLIN INJECTIONS IN ALLERGIC CHILDREN

SAMUEL J. LEVIN, M.D., F.A.C.A., and
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Detroit, Michigan

THE purpose of this paper is to report our experiences with repository penicillin injections, administered for acute infections in allergic children. Numerous reports seem to indicate that considerable apprehension exists as to the danger of sensitization reactions to penicillin, occurring particularly in the allergic patient,[7] following penicillin injections. Several deaths in adults[11] following penicillin injections, one in an allergic individual,[10] have furthered this impression.

It was recognized early in the use of repository penicillin that untoward reactions occurred in a considerable number of patients following its administration. Such reactions undoubtedly were due in part to the beeswax used originally in the Romansky formula.[9] Subsequently with the development of other types of repository penicillin it was felt that impurities in the penicillin itself might be partly responsible for sensitivity reactions, since it has been observed that a patient may be clinically allergic to one preparation of penicillin and not to another. However, even with the purer crystalline forms of penicillin now available, sensitization reactions occur. Thus Lepper and his associates[7] point out that 1.2 per cent of their patients receiving the crystalline form of procaine penicillin G in aqueous solution became clinically sensitive, while 1.4 per cent became sensitive to the procaine penicillin G in oil. They also point out that with large doses of the crystalline penicillin in aqueous solution the sensitivity rate jumps to 7.8 per cent and also that repeated administration tends to increase the incidence of reactions. Most reports of sensitivity, however, have to do with adult patients. Judging from reports in the literature, sensitization to penicillin seems to occur much less frequently in children than in adults. Thus Adams and Fisher,[1] using the old Romansky formula of procaine penicillin G in oil and beeswax, reported that in 180 children no general allergic reactions occurred, and only a few mild local reactions were seen. Our own experience with the beeswax preparation was not so happy. Numerous local reactions and an occasional general reaction characterized by hives, and in some cases enlarged glands and joint swellings, caused us to abandon the use of the Romansky formula very early. Others,[2,3,4,5] using procaine penicillin G suspended in oil and 2 per cent aluminum monostearate in large series of children with various infections, found a paucity of sensitization reactions. Peck and his

In part from the Allergy Clinic of the Children's Hospital of Michigan, Detroit, Michigan.
Presented at the Seventh Annual Congress, American College of Allergists, February 11-14, 1951, Chicago, Illinois.
Approved for publication April 5, 1951.

associates,[10] in a very comprehensive report of their experiences with the problem of penicillin sensitivity, found three of thirty-six children clinically sensitive to penicillin (8.3 per cent), while in their series of 127 adults twenty-nine were clinically sensitive (22.9 per cent). These figures are admittedly high in the light of more recent experience indicating that at present a much lower rate of sensitization to procaine penicillin occurs, probably as a result of the use of the more highly purified crystalline forms. However, Peck's figures do substantiate again the much lower tendency for children to become "allergized" to penicillin than adults.

In connection with the infrequency of penicillin reactions in children, the figures of the Children's Hospital of Michigan are of interest. During the past five years thousands of injections of repository procaine penicillin G have been administered to many hundreds of children both as in-patients and out-patients. During this period not a single child developed a sensitization reaction worth noting.[12] Many of these patients received several courses of penicillin at wide intervals. Most of these children, however, were patients in the general clinics and wards of the hospital, and in the main were not allergic individuals. The question therefore arose early in our use of penicillin as to whether allergic children were more liable to become sensitized to penicillin than nonallergic children. Our experience with an estimated 1,000 repository penicillin injections in 226 allergic children during the past three years is of interest in this connection.

### TYPES OF REPOSITORY PENICILLIN USED

When the only repository penicillin available was the Romansky formula containing beeswax and oil, we quickly abandoned its use because of the frequent occurrence of severe local and general reactions. We subsequently used in turn as they became available the following forms of repository penicillin:

Procaine Penicillin G suspended in peanut oil with 2 per cent aluminum monostearate (Upjohn, CSC)
Procaine Penicillin G suspended in peanut oil (Upjohn, CSC)
Procaine Penicillin G suspended in sesame oil (Lilly)
Procaine Penicillin G aqueous suspension (Lilly, Upjohn)

It was our impression that the clinical benefit obtained with the aluminum monostearate preparations (so-called ninety-six-hour penicillins) was not as rapid as with the more quickly absorbed forms of repository penicillin without aluminum. Blood level studies have indicated much higher blood levels with the latter types of penicillin, and during the last two years we have discontinued the use of the aluminum preparations, relying entirely on the so-called twenty-four-hour types of repository penicillin. We have seen no clinical difference in the use of the oil or aqueous preparation of procaine penicillin G. After procaine penicillin G in aqueous suspension became available, we used this preparation exclusively, since no

advantage could be gained by administering a preparation containing either peanut or sesame oil parenterally, despite lack of evidence as to the purified oils being antigenic.

A great deal of literature has accumulated indicating that repository penicillin injections are effective for most of the secondary invaders in the common respiratory infections in children. Several studies on blood levels after the administration of procaine penicillin G in oil or in aqueous suspension seem to indicate that in general 1 cc of either preparation every twenty-four hours provided adequate blood levels in most children.

### INDICATIONS FOR THE USE OF REPOSITORY PENICILLIN INJECTIONS IN ALLERGIC CHILDREN

Respiratory infection is one of the major causes of precipitation of asthmatic episodes. Most of the children who received penicillin in this study were asthmatic. They had all been subjected previously to a complete medical survey followed by comprehensive allergic study, including scratch and intradermal skin tests. Elimination and immunization (hyposensitization) regimes were then carried out. Despite such treatment, as is well known, respiratory infections frequently precipitate attacks of asthma, especially during the early period of treatment before antiallergic measures have had sufficient time to become effective. It occurred to us that the severity and duration of asthmatic episodes precipitated by respiratory infections might be diminished and alleviated by the early administration of repository penicillin therapy. It was our procedure to administer daily injections (1 cc per dose) of repository penicillin for several days very early in the course of such infections. Many children in this series received three or four courses of penicillin for repeated episodes. Two of the children had twenty-four injections of penicillin extending over a period of two years, and many others received ten or more. The average number of injections was four. The results have been uniformly beneficial in our asthmatic patients. Many of these were clinic patients who, because of poor economic conditions and unsatisfactory environmental control, have been difficult problems. Some of them, because of poor parental cooperation, would continue ambulatory despite respiratory infections and elevation of temperature. Prior to the free use of penicillin such patients generally developed severe attacks of asthma and often required hospitalization. Since we have begun the injection of penicillin for two or three days in succession shortly after the onset of respiratory infection in these asthmatic children, there has been a marked decrease in the severity and duration of such episodes and a marked reduction in the development of status asthmaticus.

Approximately thirty of the children who received penicillin were seen because of allergic rhinitis and a tendency to the frequent development of respiratory infections. These children often develop purulent sinusitis as a result of poor nasal drainage, and a number were susceptible to middle

ear infection with each episode. We have found that repository penicillin injections at daily intervals for several days were very effective in shortening the duration and severity of such complications.

Fifteen of the patients in this series were infants and children with various types of skin infection including impetiginous eczema, furunculosis, and episodes of lymphadenitis and fever. Most of these patients responded rapidly to several daily injections of respository penicillin.

It is not surprising that the open skin in eczema cases becomes infected. It is to be wondered at that such superimposed infections do not occur more frequently considering the great opportunity for infection as a result of continuous scratching and the destruction of the integrity of the epidermis.

### SENSITIVITY REACTIONS

No evidence of sensitivity to penicillin occurred in the entire group of 226 children except one who developed a transient pruritic erythema which lasted only twenty-four hours. This child had previously received one injection of penicillin. Subsequently, skin tests with penicillin and Trichophyton were negative in this patient.

### SKIN TESTS WITH PENICILLIN AND TRICHOPHYTON

The possibility that fungus infection of the skin might be the sensitizing mechanism in certain patients sensitive to penicillin has been investigated by Peck and his associates.[8] They determined that positive skin reactions to penicillin occurred spontaneously (without prior penicillin injections) three times as frequently in those adults reacting to the Trichophyton skin test than in those that were negative to Trichophyton. None of the sixty-five children in their series (of whom thirty-six had received penicillin previously) reacted to Trichophyton by skin test. Of the thirty-six children who received penicillin, three were clinically sensitive to penicillin but only one reacted to penicillin by skin test.

We carried out skin tests for both penicillin and Trichophyton on forty of the children in our series who had received from three to six penicillin injections several months previously. The tests were performed according to the method of Peck, modified as follows: 1,000 units of penicillin in .05 cc normal saline was injected intradermally. At the same time, .05 cc Trichophyton extract (Lederle) 1:30 was also injected intradermally. Readings were made in ten minutes and in twenty-four hours. No immediate reactions of the wheal type occurred to either penicillin or Trichophyton, even in the child mentioned above who gave evidence of mild penicillin sensitivity. In one child not clinically sensitive to penicillin a moderately positive twenty-four-hour delayed reaction to penicillin occurred. Two children with chronic atopic eczema (chronic infectious eczematoid dermatitis) and one with asthma gave positive delayed reactions to Trichophyton.

## DISCUSSION

It is evident from the data presented that sensitivity to the purified forms of crystalline procaine penicillin G is extremely rare in children. It is also apparent that even allergic children are unlikely to develop sensitivity reactions. That such is not the case in regard to adults is obvious to any clinician dealing with older individuals. Reports of penicillin reactions continue to appear in the literature. In our private practice dealing with allergic adults as well as children, we have seen sensitivity to penicillin develop in several adults. We have also seen a number of adult patients referred to us for treatment of severe penicillin reactions, but during the same period of time we have not seen any penicillin reactions among children.

It should be kept in mind that sensitization can occur to practically any substance, drug, or medicament. It is therefore to be expected that despite the rare tendency of penicillin to sensitize children, such sensitivity is to be expected and will be encountered occasionally. Our experience may have been a particularly fortunate one in this regard. That severe reactions to penicillin in children can occur is borne out by the experience related by Figley.[12] He was called to see a child *in extremis* with severe asthma. This patient had received two prior injections of penicillin, each producing slight but increasing wheezing. Following the third injection it was necessary to call the Rescue Squad to resuscitate the child, whose anaphylactoid type of reaction was almost fatal. Peck's postulation that prior fungus infection prepares the groundwork for future penicillin sensitization seems a possible explanation. However, positive reactions to Trichophyton do occur in children. In the forty children tested in this series three gave positive reactions to Trichophyton (7.5 per cent). Others have reported positive skin tests to Trichophyton in children of lower but significant percentage. It seems to us that the explanation of the greater tendency to penicillin sensitivity in adults may be due not only to the greater number sensitive to fungi but also in part to the longer duration and/or greater activity of the fungus infection. The older the individual, the more likely the possibility of such long standing, persistently active fungus infection resulting in fungus sensitivity.

## SUMMARY

1. Approximately 1,000 injections of repository penicillin were given to 226 allergic children. The average number of injections per patient was four. Several children received as many as twenty-four injections.

2. Injections of repository penicillin have been a valuable adjunct in the treatment of respiratory infections in asthmatic children. It has shortened the duration and severity of such episodes and decreased the incidence of status asthmaticus. It has also been effective in other infections occurring in allergic children.

3. No important local or general sensitization reactions were observed other than one transient pruritic eruption in one patient.

4. The clinical results using procaine penicillin G in oil or in aqueous suspension seemed to be superior to the procaine penicillin G in oil and aluminum monostearate.

5. Sensitization to penicillin is extremely rare in children. Allergic children are apparently no more liable to sensitization to penicillin than are nonallergic children. Repeated administration did not seem to increase the liability to sensitization.

6. Skin tests for penicillin and Trichophyton in forty penicillin-treated children were carried out. One child gave a positive delayed reaction to crystalline penicillin but was not clinically sensitive. Three children reacted to Trichophyton (7.5 per cent).

7. The low incidence of penicillin sensitivity in children as compared to adults may be explained in part by the relative infrequency of fungus sensitivity in younger individuals. It is possible that the activity and duration of fungus infections are important in mediating such sensitivity and may account for the much greater incidence of penicillin sensitivity in adults.

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*469 Fisher Building.*

# SPONTANEOUS ANIMAL ALLERGY

## Report of a Case

LEON BENTOLILA, M.D., F.A.C.A., and SOL L. RABASA, M.D.
Rosario, Argentina

SUFFICIENT evidence has been reported that the terms *allergy* and *atopy* signify specifically altered reactivity not only in man, but also in lower animals. *Allergy,* as was discussed in a paper by one of us in 1944,[3] should be used to signify phenomena of acquired specific qualitatively altered reactivity in man and lower animals. *Hypersensitiveness* should be used to signify quantitatively altered reactivity. In the consideration of these phenomena we usually follow Forman's classification, as modified by Sulzberger.

Coca's[1] term *atopy,* according to his own definition, means "certain clinical forms of human hypersensitiveness that do not occur, so far as is known, in the lower animals and which are subject to hereditary influence." The possibility of atopy existing in animals is left open in this definition by the words "so far as is known." Phillips'[2] observations in 1922 that certain foods caused angioneurotic edema in dogs; Schnelle's[4] paper published in 1932, showing that dermatitis in dogs can be produced by an allergic mechanism; and later papers by Burns, Pomeroy, and others, are evidence pointing to the existence of atopy in lower animals.

Wittich[5] in 1941 reported a case of respiratory localization of atopy allergy in dogs, and later, similar observations were made by Thomas, Ruiz Moreno and Bentolila, Wittich, and others.

The object of this paper is to add yet another observation to the numerous list so far reported and thus to contribute evidence necessary for a final decision on the terminology to be used in these cases.

### CASE REPORT

A seven-year-old gun-dog was found suffering from permanent rhinopathy of several years' standing, soon complicated by signs of bronchial spasm. The animal had frequent attacks of marked expiratory dyspnea, which at times, owing to its duration and severity, became the equivalent of status asthmaticus. Antispasmodic drugs had little or no effect, and the general condition of the animal deteriorated progressively.

The blood count showed moderate anemia. The white blood count showed 12 per cent eosinophiles, but similar figures (11.5 to 13 per cent) were found in normal animals. While we were trying to obtain nasal secretion for a smear, the animal died suddenly.

*Postmortem Examination.*—The lungs appeared considerably increased in size due to distention of approximately nine tenths of the lungs. They were soft and crepitating. Microscopical examination of paraffin sections stained with hemalun-eosin, and taken from apparently normal parts of the lungs, showed relatively normal

Approved for publication April 5, 1951.

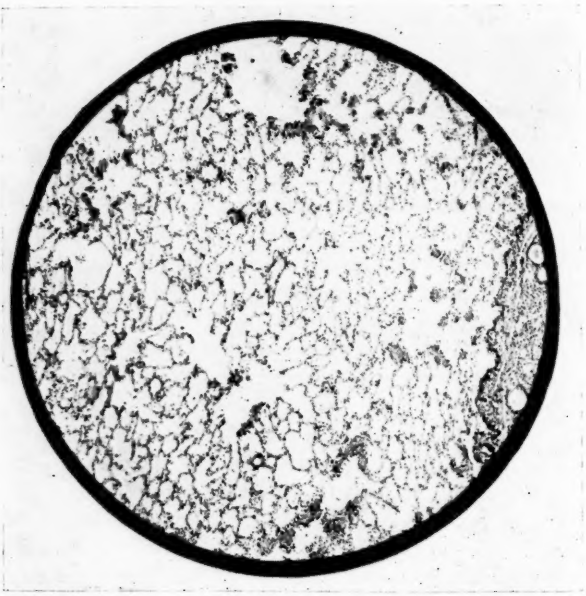

Fig. 1. Specimen taken from macroscopically normal lung tissue. Some of the alveolar walls are destroyed, and there is evidence of bronchial inflammatory reaction.

Fig. 2. Emphysema, with considerable destruction of alveolar walls.

Fig. 3. Inflammatory reaction in bronchi. Intense infiltration in the bronchial walls and lumen filled by mucus and cells.

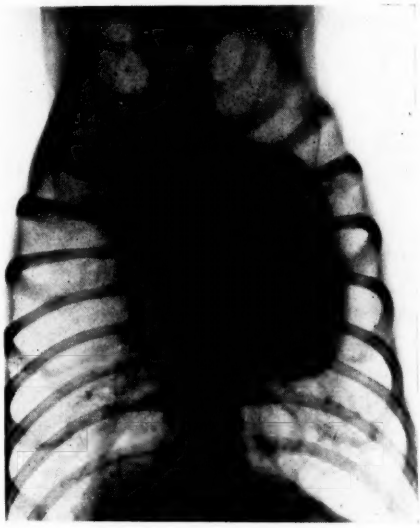

Fig. 4. X-ray of lungs.

alveoli (Fig. 1) and intense inflammatory reaction in the bronchi with mucus and cellular exudate in the lumen and infiltration of the walls by lymphocytes, plasmocytes and histiocytes (Fig. 3). The lumen of the bronchi was not decreased, and there was no folding of the mucosa. Eosinophile infiltration of the lung tissue was not observed. The parts which were distended showed large vesicles formed by confluence of several alveoli owing to destruction of alveolar walls. The remaining partitions were much thicker than the normal (Fig. 2).

## COMMENTARY

When alive the animal suffered from a typical asthmatic syndrome. The high eosinophile count cannot be considered significant because it was also found in normal dogs. Death occurred suddenly when the animal was not in the midst of an attack of asthma, and signs of bronchial spasm were not found in the postmortem examination. The sequelae of its pulmonary condition were, however, fully developed: there was marked emphysema, intense bronchitis with abundant mucus and numerous cells in the lumen, and infiltration of the bronchial walls by lymphocytes, plasmocytes, and histiocytes.

## SUMMARY

A dog with a typical asthmatic syndrome (attacks of intense expiratory dyspnea) was observed. Postmortem examination showed the sequelae of chronic bronchial disease. This case is further evidence that the term *atopy* can be used correctly in referring to allergic conditions occurring spontaneously in lower animals.

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*San Lorenzo 1150*

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## COMMUNICATION

C. D. W. Stafford, Managing Director
C. L. Bencard, Ltd.,
Great West Road, Brentford, Middlesex
England

Dear Mr. Stafford:

Referring to your letter of June 18, to Dr. French K. Hansel, regarding statements made in my Presidential Address to the Seventh Annual Congress of The American College of Allergists, appearing in *Annals of Allergy*, March-April, 1951, pages 230-235. You point out readers might infer that the terms "inhalant mixture" and "Bencard's Mixture" are identical. You further feel that the reference to the solution of inhalant proteins as Bencard's Mixture might possibly cast some unfavorable reflection upon the status of your company. In rereading the address I realize you are quite correct in your objection. During my visit to London I gained the impression that the inhalant protein mixture and Bencard's Mixture were preparations of similar composition and content though perhaps not identical and that Bencard's Mixture was a proprietary preparation. In the experiments referred to on page 233, mixed inhalant protein was used and, therefore, the words Bencard's Mixture should be deleted.

I hope you will forgive my unintentional error.

A copy of this letter is being sent to Dr. Hansel, Editor-in-chief of the *Annals of Allergy*, for publication in the next issue.

Sincerely yours,
JOHN H. MITCHELL, M.D.

July 5, 1951

# THE CLINICAL EVALUATION OF AMBODRYL HYDROCHLORIDE

## A Report of 100 Cases

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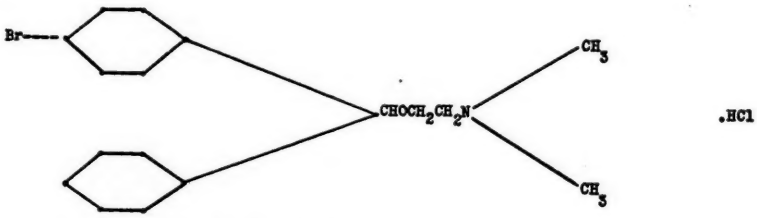
SINCE Benadryl and Pyribenzamine were first employed and blazed the trail for the subsequent antihistamines, we have all appreciated the importance of this group of drugs used in the control of symptoms from varied allergic manifestations.

There have been reactions sufficiently disagreeable to warrant a further search for an antihistamine that would have fewer side reactions. This has been accomplished to some extent, and progress has been made by various research groups. These products have appeared on the open market with encouraging results.

As Brown and Krabek[1,2,3] have made such an extensive review of the literature covering antihistaminic agents, giving complete references, no further discussion will be made of them in general; and we are limiting this paper to the clinical evaluation of a new antihistamine.

Synthesized by the Department of Clinical Research of Parke, Davis & Company, Ambodryl Hydrochloride, previously known as antihistamine compound No. 890, is chemically designated as B-(4-bromobenzohydryloxy)-ethyl-dimethylamine hydrochloride and has the following structure:




It is a white crystalline compound readily soluble in water in excess of 5.0 per cent concentration. It has a very bitter taste.

Oral treatment studies were made by Parke, Davis Research Department[4] parallel with Benadryl Hydrochloride in albino rats initially, and it was found that Ambodryl Hydrochloride was a less toxic substance in mice orally and in rats intravenously in comparison with Benadryl Hydro-

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The Ambodryl Hydrochloride employed in this study was supplied through the courtesy of Dr. E. A. Sharp, Director of Department of Clinical Investigation, Parke, Davis & Company.

From The Thomas Clinic, Richmond, Virginia.

Presented at the Seventh Annual Congress of The American College of Allergists, February 12, 1951, Chicago, Illinois.

TABLE I. SUMMARY OF RESULTS OF AMBODRYL THERAPY IN 100 PATIENTS SHOWING VARIOUS ALLERGIC MANIFESTATIONS

| Allergic Manifestation | Number of Patients | Dosage per Day in mg | Days of Therapy | Satisfactory Response | Ambodryl Tolerated | Ambodryl not Tolerated |
|---|---|---|---|---|---|---|
| Rhinitis | 51 | 10-200 | 1-180 | 40 | 44 | 7 |
| Hay fever | 5 | 10-200 | 1- 60 | 2 | 4 | 1 |
| Asthma | 4 | 10-100 | 5- 60 | 1 | 3 | 1 |
| Asthma and rhinitis | 10 | 100-200 | 1- 30 | 8 | 8 | 2 |
| Asthma and hay fever | 4 | 100 | 5- 30 | 3 | 3 | 1 |
| Urticaria and angioneurotic edema | 5 | 100 | 5-120 | 4 | 5 | 0 |
| Dermatoses | 16 | 100-200 | 3- 90 | 12 | 12 | 4 |
| Miscellaneous | 5 | 10-200 | 14-180 | 5 | 5 | 0 |
| Total | 100 | 10-200 | 1-180 | 75 | 84 | 16 |

chloride when given in single doses. Initial experience is encouraging, and a favorable comparison has been made with Benadryl in studies on laboratory animals. The dose of 25 mg seems to be comparable to a 50 mg dose of Benadryl Hydrochloride in humans.

The clinical investigation of Ambodryl Hydrochloride was prompted by our appreciation of the desirability of having available an antihistamine which produced minimal side effects, and one from which our patients would find symptomatic relief in varied allergic manifestations. This study was carried out in patients who had had previous antihistaminic drugs as well as patients who gave no history of previous antihistaminic therapy.

Table I is a summary table of a correlation of the number of patients having varied allergic manifestations; it reveals range of dosage, days of therapy, and results of therapy, and indicates the number of patients who tolerated or did not tolerate Ambodryl Hydrochloride.

Those patients having respiratory manifestations of allergy were divided into five groups: (1) perennial allergic rhinitis, (2) bronchial asthma, (3) hay fever, (4) bronchial asthma and perennial allergic rhinitis, (5) bronchial asthma and hay fever (seasonal). Of the 100 total cases studied, this group represented seventy-four cases, or 74 per cent, having involvement of the respiratory tract.

The group of patients having perennial allergic rhinitis, seasonal hay fever, perennial allergic rhinitis and asthma, and hay fever and asthma totalled seventy cases; and of these, fifty-three patients (75.7 per cent) appreciated a satisfactory response to Ambodryl, and eleven (15.7 per cent) were unable to tolerate the drug. Seventy-five per cent of seasonal asthma and hay fever cases, and 80 per cent of asthma and rhinitis cases having combined symptoms appreciated a satisfactory response to treatment.

The result of therapy in the fifty-six patients having either perennial or seasonal nasal symptoms is found to be satisfactory in forty-two (75 per cent), and eight (14.3 per cent) of this group did not tolerate Ambodryl and exhibited one or more reactions, characterized by drowsiness or

nervousness, and it was necessary to discontinue the drug. The majority of this group of patients were able to get satisfactory relief on a dosage of 25 mg four times a day; however, there were certain patients who required larger dosages and were given 50 mg four times a day. Some in the younger age group were given as little as 10 mg per dose. This was usually prepared in the form of a syrup containing 10 mg per dram given every four hours.

As this drug was not supplied in an elixir form, it was necessary that we prepare a prescription which contained Ambodryl, 300 mg, glycerine, 10 cc, simple syrup, qs ad 120 cc. The rhinitis group was under treatment for periods of time up to six months, as one might expect in those patients having perennial symptoms, and the hay fever group represented those patients whose therapy extended from one day to two months, including one or more of the pollinating seasons.

Those patients having a combination of asthma and rhinitis, or a seasonal bronchial asthma and hay fever, totalled fourteen. Eleven (78.5 per cent) obtained a satisfactory response to the drug, and three patients (21.4 per cent) had side effects. It was interesting to observe that in these various manifestations treated certain of the patients stated that they obtained a satisfactory relief of symptoms but that the side reactions from the drug were so disturbing that they preferred to have the rhinitis or asthma, whichever the case might be, rather than to be subjected to the therapy. There were other patients who obtained no relief of symptoms and who also exhibited side reactions which were annoying.

Only one of the four cases with asthma showed a satisfactory response to treatment. This was a child, aged two, who received 10 mg of Ambodryl four times a day for a two-month period in spite of a slight reaction characterized by anorexia, insufficient to discontinue the drug. Incidentally, this patient did not tolerate nor receive benefit from other antihistamines previously taken.

Those patients having skin manifestations of allergy were divided into two groups as follows: (1) urticaria and angioneurotic edema occurring separately or together in the same patient; (2) dermatoses, which include those patients manifesting, separately or in combination, one or more complaints such as atopic dermatitis, contact dermatitis, pruritus vulvae, dermatitis medicamentosa, allergic conjunctivitis, and pruritus ani. Some of these patients, in addition to their dermatoses, had either asthma or rhinitis or both. These two groups comprised 21 per cent of the total cases. All of the urticaria and angioneurotic edema patients tolerated the drug, and 80 per cent received satisfactory relief; 75 per cent of the dermatoses group were benefited; and four patients showed reactions.

The miscellaneous group represented patients exhibiting headache, gastrointestinal allergy, rhinitis, with associated cough or allergic bronchitis; and certain of these patients had additional manifestations including seasonal hay fever, perennial allergic rhinitis, and bronchial asthma. This

group included only 5 per cent of the total study. All patients were benefited and no reactions were experienced.

In general, a larger number of patients (84 per cent) tolerated the drug than the number of patients (75 per cent) who obtained a satisfactory response to treatment. Only 16 per cent of the entire group of 100 cases were found to show an intolerance or side reaction to this drug. Of the total number of seventy-five patients who appreciated a favorable response to therapy, fifty-six reported very favorable or excellent relief of their symptoms, and nineteen had a fair response to the drug.

TABLE II. A COMPARISON OF AMBODRYL TOLERANCE WITH THAT OF A HISTORY OF TOLERANCE TO OTHER ANTIHISTAMINES CONSIDERED AS A GROUP—ALL PATIENTS DID NOT HAVE PRIOR THERAPY WITH OTHER ANTIHISTAMINES IN ADDITION TO AMBODRYL

| Tolerance | Number of Patients |
|---|---|
| Ambodryl tolerated | 84 |
| Ambodryl not tolerated | 16 |
| Ambodryl and other antihistamines tolerated | 37 |
| Ambodryl tolerated, other antihistamines not tolerated | 23 |
| Ambodryl not tolerated, other antihistamines tolerated | 3 |
| Ambodryl and other antihistamines not tolerated | 4 |

We note from Table II that of the eighty-four patients who tolerated Ambodryl, thirty-seven stated they had taken other antihistamines which they had tolerated satisfactorily. We further observed that of the group of eighty-four patients, twenty-three could tolerate Ambodryl but could not tolerate other antihistamines. Three of the patients of the series could not tolerate Ambodryl but did tolerate other antihistamines satisfactorily.

TABLE III. TYPES OF REACTIONS TO AMBODRYL

| | |
|---|---|
| Drowsy* | 10 |
| Nervousness* | 7 |
| Gastrointestinal discomfort | 1 |
| Anorexia | 1 |

*3 patients experienced both of these side reactions.

As noted in Table III, the side reactions were drowsiness, nervousness, gastrointestinal discomfort, and anorexia. Three of the patients had multiple reactions. The most frequent side effect was drowsiness in ten cases, and in seven cases nervousness was noted.

Table IV shows that 40 per cent of the patients were in the fourth and fifth decades, and 83 per cent of the cases were represented by the first five decades. Our youngest patient was age two, and our oldest patient was seventy-six years old.

The sex distribution was approximately equal, in that there were forty-nine males and fifty-one females.

The majority of the cases (73 per cent) received 25 mg Ambodryl four times daily or 100 mg per day, as indicated in Table V.

TABLE IV. DISTRIBUTION OF AGE OF PATIENTS BY DECADE FROM AGE 2 TO 83 YEARS

| Decade | Number of Patients |
|---|---|
| 1 | 14 |
| 2 | 13 |
| 3 | 16 |
| 4 | 20 |
| 5 | 20 |
| 6 | 10 |
| 7 | 6 |
| 8 | 1 |

TABLE V. NUMBER OF PATIENTS RECEIVING AMBODRYL IN MG PER DAY

| Ambodryl in Milligrams | Number of Patients |
|---|---|
| 10-80* | 6 |
| 25-50 | 9 |
| 100 | 73 |
| 200 | 12 |

*Syrup of Ambodryl—Mg $\overline{\times}$ per dram.

Certain of the patients required 200 mg of the drug daily, comprising four cases of perennial rhinitis, two cases of hay fever, two cases of asthma and rhinitis, twenty cases of dermatitis, and two cases in the miscellaneous group.

TABLE VI. SHOWING THE LENGTH OF TIME IN DAYS PATIENTS RECEIVED AMBODRYL

| Days of Therapy | Number of Patients |
|---|---|
| 1 | 9 |
| 5 | 39 |
| 14 | 11 |
| 30 | 14 |
| 60 | 13 |
| 90 | 2 |
| 120 | 3 |
| 150 | 3 |
| 180 | 6 |

Table VI correlates the duration of therapy in days. Six patients received therapy over a six-month period, and nine cases received therapy for only one day; several of the patients who had significant side reactions took only one or two doses. The largest number of patients (39 per cent) received only five days of therapy.

SUMMARY AND CONCLUSIONS

1. A clinical appraisal of a new antihistaminic drug has been made in 100 private patients, with varied allergic manifestations, including perennial allergic rhinitis, hay fever, asthma, urticaria, angioneurotic edema, allergic dermatoses, and a miscellaneous group.

2. Of the group studied, 75 per cent showed satisfactory response, and 84 per cent tolerated the drug.

3. The optimum dosage in the adult group was 100 mg daily, and in children the dosage averaged 40 to 80 mg daily.

4. From the limited number of cases studied, it may be concluded that Ambodryl Hydrochloride is a satisfactory antihistaminic drug with minimal significant side reactions.

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## STANDARDIZATION OF DUST EXTRACTS

*(Continued from Page 470)*

particle agglutination tests with the sera of these rabbits and by skin sensitivity tests on these animals. The results of these tests on six dust extracts have been compared with the reactivities of these extracts on the skins of dust-sensitive human beings. This comparison has revealed that there is no quantitative relationship between the serological or the rabbit skin sensitivity titers and the human skin sensitivity titers of the six extracts tested. There is, however, a qualitative correlation between the serological reactions and the human skin reactions, the very strong (crude) extracts giving strong reactions by both tests and the very weak extracts (absorbed concentrated) weak reactions by both tests. This qualitative correlation might be of some value in culling out newly prepared dust extracts which might not be potent enough to give positive skin reactions in a large majority of dust-sensitive people.

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# THE PRESENT STATUS OF PEDIATRIC ALLERGY

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ALLERGY is pervading more and more fields of medicine. Its prevalence increases not only because it is being recognized, but because living is becoming more and more complicated. Allergy is intimately associated with new contacts—new foods, new furniture, clothing, new drugs, new antibiotics, new organic products. Extensive pollination, resulting from cultivation of lands, brings in its wake a greater incidence of hay fever.

While the notion that children will outgrow their allergies is true in many cases, the fact that 10 per cent of the general population suffer major allergic manifestations and the fact that more than 50 per cent of adult sufferers date their allergy back to childhood must lead to the conclusion that allergy is not altogether a self-limited disease.

The physician may have helped to foster the notion that children outgrow allergy because he had difficulty in coping with the treatment of the syndromes encompassed in this field. It may also be that the elaborate diagnostic procedures consume more time than he can allot, commensurate with the compensation he receives. In this day of specialization, if a large fee is involved, people tend to seek the advice of the specialist. This situation is not confined to allergy alone.

Shortcuts have been sought but have not always been effective. A simplification of treatment may be brought about by an understanding of the prophylactic measures available. The happy aspects of allergy are that if treated properly a patient is left with no stigma, and second that prophylaxis is a possibility.

At present, large sums are being expended for research in infantile paralysis, tuberculosis, rheumatism and heart disease, cancer, prematurity, and so forth. Allergy affects as many children as do any one of these, yet there is practically no money being expended on its study. The reason for this is that death seldom results from allergy, despite its incapacitating and chronic character.

In such chronic diseases, it is not only the somatic changes but the psychic ones which should cause us concern, particularly in the vulnerable period of childhood. Recurrent attacks with intervening intervals of freedom are characteristic of allergic episodes. Allergic children begin to feel that they are set apart, more especially because parents tend to become overprotective and limit their activities even if these children are physically capable of joining in them. On the other hand, children take

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Presented at the Seventh Annual Congress of the American College of Allergists, February 11-14, 1951, Chicago, Illinois.
Approved for publication April 23, 1951.

advantage of the situation and use their illness in many instances as a weapon to seek more attention and to avoid responsibility.

Hence, I feel strongly that the time is ripe for an all-out effort to tackle the problem of allergy in childhood, at which time the greatest good can accrue not only to the children but to succeeding generations of adults. A preventive program could be promulgated such as has been consummated in the past two decades against infectious diseases.

Allergic manifestations arise from an altered yet physiological reaction to substances which normal individuals tolerate without difficulty. The basic mechanism is closely allied with the process of immunity.

At this time, when the histamine concept has gained such general popularity, it may be well for some of us to emphasize the importance of the immunologic basis of the hypersensitive phenomenon and to reiterate the three accepted fundamental criteria set forth for allergy: (1) the dependency upon substances known to be antigenic; (2) specificity; (3) participation of antibodies.

The amelioration of allergy depends on the ability of the body to produce enough antibodies so that they may be forced out of the cells in which they are formed and enter the general circulation, there to act as blocking or neutralizing substances against invading antigens. To this end immunizing agents must continually be manufactured.

Other therapeutic avenues have been sought. Today, we are living through the era of the so-called antihistaminic drugs. I believe I am justified in stating that clinical trial has given us some evidence of their accomplishments. They have proved to be effective in the alleviation of symptoms of pruritus, nasal and lachrymal secretions, and edema. But—and this is a large "but"—they have failed to relieve asthma or the more serious forms of dermal allergy which are the graver and more frequent manifestations in the field of allergy.

Greater emphasis, it seems to me, should be laid on prosecuting further studies in the lower animal with these drugs. Several groups of investigators have published work which showed that although antihistamines almost uniformly prevented the intoxicating symptoms of histamine shock from occurring in the lower animal under experimental conditions, they failed to prevent specific anaphylactic shock symptoms from occurring in rabbits and guinea pigs sensitized and shocked with egg white. Whether this work will be corroborated or refuted in the future will be watched with interest.

From their mode of action, it is obvious that these drugs act only as palliative agents, but they do not eliminate the basic mechanism responsible for allergic symptomatology.

We are not prepared, as yet, to evaluate the roles of ACTH and cortisone.

Bearing in mind the three facets of the hypersensitive phenomenon—antigenicity, specificity and antibody participation, I cannot envisage a

single drug or substance of any kind which might be capable of destroying the specific antigen-antibody mechanism and yet not destroy the organism as a whole, because of the basic relationship between allergic and immune processes.

It is my contention that the more productive and hopeful approach for therapy and prophylaxis in this field is through the study of the ways and means that antigens have of invading the body and producing interreactions with the tissue-fixed antibodies. The control and correction of the environment, of highly antigenic food excesses, of promiscuous and thoughtless use of sera and drugs, and control of diseases which tend to increase the permeability and dysfunction of our protecting membranes are measures which tend to reduce the incidence of allergy.

For the time being, the treatment of the patient still entails a search for offending substances, their elimination or reduction, and a definite program for building up tolerance. Increasing understanding of basic principles and prophylactic measures may reduce the need for elaborate studies, especially in certain cases which lend themselves to ready and early diagnosis.

In the early days of the recognition of allergy, there was much fanfare about the difficulty of performing skin tests, and patients were referred from great distances to the then handful of allergists. They tested the patients, prepared protein mixtures, and sent them to the local physician with instructions for administration. Many cases were helped by this procedure, particularly those suffering from hay fever. However, it was, and is, difficult to lay out a successful plan for the treatment of severe eczema or asthma.

Where are we heading, therefore, in the clinical practice of allergy? Are we giving the best to each patient? Are we practicing allergy as it should be? Why are allergists frowned upon? Well, there are at least two major reasons:

1. It is claimed that they do little to benefit the patient.
2. It is claimed that they have done too well by the patient.

The referring physician wants the allergist to serve in the capacity of technician. He would have us do some tests and send back a set program for treatment. It would be fine if we could lay out a blueprint for each case. But this is not easily done. No blueprint comprehensive enough to cover unpredictable eventualities can as yet be drawn.

In our evaluation of a case, consideration must be given to careful history, physical findings, constitutional factors, endocrine and psychosomatic factors, blood studies, nasal cytologic studies, and fluoroscopic and roentgenologic findings, in addition to careful skin testing. What is more, many of these findings are not static but undergo change. It is the evaluation of these changes which makes for proper orientation and treatment.

In the case of respiratory allergy, for example, one may discover an infectious sinusitis, or an allergic or bacterial pneumonitis. A cytologic change in the nasal secretion might point to an allergic or infectious episode. Yet to the casual observer all of these episodes would be symptomatologically diagnosed as allergic. Treatment on such a basis would be ineffective. Each incident must be carefully differentiated and treated on its own basis. The same may be said of dermal allergy. One episode may be allergic in origin, another might be due entirely to secondary infection. By the same token a dermal reaction may be related to a hypothyroidism or be psychosomatic in origin.

With respect to the skin tests, they are not by any manner of means the all-encompassing diagnostic tool in allergy. Without benefit of the skin tests, however, I doubt whether allergy would have made the strides it has. They have guided us by focussing attention on etiologic factors. We have been able to state with a fair degree of assurance that one individual is sensitive to egg white and another to ragweed. Nevertheless, the skin test is fallible. At times the skin is insensitive, and there are many other problems involving antibody fixation and chronological and topical relations. As the child progresses new skin sensitivities may arise which were not present at the time the child was originally tested. Yet with all its inadequacy and imperfection it is the best we have and compares favorably with other biological methods of diagnosis.

It takes years of experience even for the trained allergist to analyze and track down each allergic episode. It is therefore asking the impossible for the allergist to send detailed instructions to the referring physician to encompass so enigmatic a condition.

The only solution I see is for all pediatricians to become well versed in allergy. It has been an encouraging sign that since the inception of round tables at the Academy of Pediatrics meetings, those on allergy have always been promptly oversubscribed. We take this to indicate that pediatricians feel the need to learn about this subject.

As time goes on and increasing knowledge of the ways of allergy develops, much prophylactic work will be done. The control of the environment and the reduction of food allergy by the proper use of heat-denatured foods will go a great way in reducing the incidence of allergy. Early recognition of symptoms and prompt treatment will reduce materially the development of chronic allergy.

A joint effort must be made by the pediatric allergist and pediatrician. The allergy case must not be treated solely symptomatically. The parents must be educated and taught how to handle minor episodes. Preventive measures must continually be emphasized. Immunologic and psychosomatic treatment, as well as proper general care, build these children up so that allergic episodes disappear almost entirely, if not entirely, and the general well being of the child is improved. I know of no disease

*(Continued on Page 516)*

# CLINICAL EXPERIENCE WITH CHLOR-TRIMETON MALEATE REPEAT ACTION TABLETS AND TRIMETON MALEATE TOPICAL 5 PER CENT

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CHLOR-TRIMETON MALEATE RFPEAT ACTION TABLETS*

CHLOR-TRIMETON MALEATE 8 mg Repeat Action Tablet is the brand name for chlorprophenpyridamine maleate. Each coated tablet contains 8 mg 1-parachlorophenyl-1-(2-pyridyl)-3-dimethylamino-propane maleate, 4 mg for immediate action and 4 mg coated for delayed action.

Previous clinical reports on Chlor-Trimeton Maleate have uniformly shown that it is very effective therapeutically and has comparatively little toxicity. Side reactions are negligible. The Repeat Action Tablet is a combination of a tablet consisting of an outside coating which allows almost immediate absorption and an inner coating which produces a delayed absorption.

In the present study, the Repeat Action Tablets of Chlor-Trimeton Maleate 8 mg were administered to 100 office patients. By far the majority of these suffered from perennial bronchial asthma, of which a proportion presented seasonal exacerbations. The duration of the disease was from eighteen months to twenty years. The youngest patient was five years old, but the majority were in the fourth to the sixth decade of life. Owing to the extreme changes in temperature and the rugged climate of the middle northwest and Pacific northwest, many of these patients also had a superimposed infectional element. Patients found sensitive to inhalant allergens were receiving standard immunization injections and, where a food sensitivity was demonstrated, they had been placed on a prescribed diet.

It has been our experience that in this region many of the patients with seasonal hay fever also have either perennial or seasonal asthma and others have mixed or infective asthma. Seventy-five per cent of these also had vasomotor rhinitis. All of the patients were closely observed in private practice and the results tabulated from time to time on successive visits. The more severe cases required one tablet 8 mg three times a day, but the majority required a tablet only on arising and on retiring to obtain satisfactory relief. The onset of the effect of these tablets averaged twenty minutes, and the duration of the effect averaged eight to twelve hours.

*Kindly supplied by Schering Corporation, Bloomfield, New Jersey.
Approved for publication June 7, 1951.

Twenty of the sixty cases were complicated by pollen asthma, and forty of the total series of 100 suffered seasonal hay fever due to pollen, complicated by a perennial bronchial asthma. The tablets were available to treat only ten of the typical seasonal hay fever cases at the time of this report. Seventy-five to 100 per cent relief was obtained in half of the pollen asthma cases, forty cases obtained 50 to 75 per cent relief, and ten comparatively poor relief. Contrary to other observers concerning the poor results in bronchial asthma of mixed type, the Repeat Action Tablet gave good relief in 45 per cent, fair relief in 30 per cent, and poor relief in 25 per cent.

Of those cases with allergic vasomotor rhinitis, the majority were complicated by perennial asthma. Fair results were obtained in the large majority.

Unexpected favorable results were obtained during the winter in perennial allergic asthmatic patients who also had frequent common colds of an infective nature. Frequently these patients developed sensitivity to the sulfonamides, Aureomycin, and Terramycin; and the use of these antibiotics even in those who did not develop a sensitivity to them gave comparatively poor results in the patients with asthma complicated by colds. The patients suffering from colds were unaware that they were not receiving some form of antibiotic, and when they would catch a fresh cold they would insist on receiving the Chlor-Trimeton Maleate Repeat Action Tablet, rather than the "other" tablets (antibiotic).

Almost all of the asthmatic patients who developed typical common colds had them aborted within twenty-four hours with the Repeat Action Tablet of Chlor-Trimeton Maleate 8 mg. The infective sinusitis cases also obtained considerable relief. Nine of the patients developed a mild reaction, a slight drowsiness, with only one developing vertigo. No gastrointestinal upsets were noted. Only two discontinued the drug because of reactions, and these had previously been unable to tolerate other antihistamines. Almost all toxic symptoms disappeared after the use of the tablets for a day or two.

## *Summary and Conclusions*

Chlor-Trimeton Maleate Repeat Action Tablets 8 mg proved, in this small series, to be very effective in the symptomatic treatment of respiratory allergy, including perennial bronchial asthma and asthma associated with pollen or seasonal exacerbations. In the majority the effective dose was an 8 mg tablet twice daily. Chlor-Trimeton Maleate Repeat Action medication showed a distinct advantage over Chlor-Trimeton Maleate plain in 4 mg doses. The patients with asthma and allergic vasomotor rhinitis complicated by common colds obtained superior beneficial therapeutic results when compared with those achieved by antibiotics.

### TRIMETON MALEATE TOPICAL 5 PER CENT†

Trimeton Maleate Topical 5 per cent contains 5 per cent prophenpyridamine maleate in a water-soluble base.

A series of fifty patients suffering from various allergic diseases were treated with this cream. As a control, the bland base of the same ointment was employed. Practically all of the patients treated were under the usual avoidance or elimination measures as well as receiving immunization against inhalant offenders. This series was limited entirely to allergic patients suffering from atopic dermatitis, circumscribed neurodermatitis, contact dermatitis, urticaria, and dermatitis medicamentosa. The average duration of treatment was four months.

Fifteen patients had atopic dermatitis, seven children and eight adults. One adult developed an eczematous reaction. This may have been due to the Trimeton, since the control was negative, although it is well known that a clinical flare may occur if anything or nothing has been used.

There were ten cases of localized neurodermatitis. All of these were adults. In all of these cases there was a complete alleviation of the pruritus, and involution of the lesions was quite rapid with the exception of six cases of long standing. In the latter the lesions were not changed although the pruritus was greatly relieved.

There were nine cases of contact dermatitis, all in adults. There was satisfactory amelioration of the pruritus, with the exception of two cases where the antihistaminic ointment, but not the control, increased the irritation. These cases whose skin became worse developed the condition within two months after using.

Five cases of urticaria, four in adults and one in a child, obtained excellent amelioration of the pruritus.

Two cases of dermatitis medicamentosa were relieved of the itching, with rapid subsidence of the lesions.

### *Summary and Conclusions*

Trimeton Maleate Topical 5 Per Cent, consisting of 5 per cent prophenpyridamine maleate in a bland water-miscible base, was used in a series of fifty cases which were treated for pruritus accompanying certain allergic dermatological conditions. The bland base of the ointment was used as a control. Very satisfactory relief of pruritus was noted in the majority of cases of urticaria, atopic dermatitis, localized neurodermatitis, and contact dermatitis. In one case of atopic dermatitis and two cases of contact dermatitis the ointment increased the irritation.

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† Kindly supplied by Schering Corporation, Bloomfield, New Jersey.

# PYROMEN THERAPY IN THE TREATMENT OF FOOD ALLERGY
## A Preliminary Report

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THE purpose of this paper is to present a preliminary report dealing with observations made on 125 patients treated with Pyromen®* over periods varying from one to seventeen months. These patients exhibited varying degrees and manifestations of food allergy, diagnosis being based upon the ability to reproduce clinical symptoms by test feeding of suspected foods, after the foods had been omitted from the diet for a four-day period.[9] Inhalant studies were carried out using the scratch test technique. When inhalant injection therapy was given, the titration technique and therapy described by Rinkel[10,11,12] was used. The frequency of injections was based upon the period of relief obtained by such therapy, which usually averaged one week. Since this is a preliminary report, representative case histories—demonstrating the method of administration of Pyromen, dosages employed, and various clinical responses in the patients treated—rather than a statistical analysis will be presented.

Pyromen is a sterile, nonprotein and nonanaphylactogenic bacterial substance. It is not destroyed by autoclaving and is not removed by passing through a Berkefeld filter; it appears to be a complex polysaccharide.[6] Extensive laboratory and clinical investigation has shown it to have an extremely wide margin of safety.

When injected into humans or animals in proper dosage, Pyromen produces a transient leukopenia and eosinopenia, followed by a neutrophilic leukocytosis.[3,4,5,8,13,15,16,17] It produces a generalized stimulation of the reticuloendothelial system[7,15,16] and produces fever when given in sufficiently large doses.[1,4,7,14,16,17]

Hypertrophy of the small zona reticularis of the adrenal cortex of rabbits has been produced by small doses of Pyromen.[16] This has suggested possible stimulation of the cortico-secretory activity. This possibilty is also suggested by the observation that rats receiving the drug develop depletion of adrenal ascorbic acid.[2] Attention has been called to the fact that the effects of Pyromen on cellular elements of the blood are similar to those observed from adrenocorticotropic hormone (ACTH), cortisone, the alarm reaction, and the ingestion of allergenic foods.[8]

Large fever-producing doses were used in early phases of the clinical investigation of Pyromen. More recently, however, encouraging results have been obtained from the use of subfebrile doses. In the treatment of perennial allergic syndromes, Randolph and Rollins[8] recommended an initial intravenous dose of 1 to 2 gamma. If little or no systemic reaction occurred, the second dose, given forty-eight hours after the first, was in-

Approved for publication June 22, 1951.
*A product of Baxter Laboratories, Inc., Morton Grove, Illinois.

creased slightly. Third and subsequent doses were given as required, after termination of clinical effectiveness of the previous dose. This interval usually varied from three to seven days; at times, children obtained relief from symptoms for as long as three weeks. When an effective dosage was obtained it was usually continued unless the patient subsequently developed a constitutional reaction, in which case the dosage was reduced by 25 per cent. Most patients responded to dosages varying from 0.5 to 10 gamma, but perennial asthma and dermatitis seemed to require somewhat higher dosages. These investigators also reported that the drug was effective when administered sublingually.

In the 125 cases herein reported it should be noted that subfebrile doses were also employed.

### INTRAVENOUS ADMINISTRATION

The initial intravenous dose of Pyromen was 2 or 3 gamma. An occasional patient reported a sensation of relaxation or calm, while others experienced no systemic reaction whatever following the initial dose. Some patients experienced a mild systemic reaction characterized by fatigue, uneasiness, muscle aching, irritability or chilliness, which usually was described as a sensation of "coming down with the flu." Of interest is the fact that, during such a reaction, patients complained of pain and aching at the site of old healed fractures or injuries. When a reaction occurred, salicylates usually gave relief.

In the event of a mild systemic reaction, or no reaction, the second dose was usually increased by approximately 25 per cent and was administered forty-eight hours after the first dose. If the first dose produced a moderately severe systemic reaction, with or without fever, the second dose was reduced or given in the same quantity as the first, depending upon the degree of reaction in the patient. Tolerance seems to develop to the early doses so that, as a rule, it is necessary to make step-wise increases in the dosage until clinical improvement is obtained. The third and subsequent administrations were given after periods varying from four to seven days, depending upon duration of clinical effect. Relief of allergic symptoms and an increase in the sense of well-being sometimes followed the first administration but, more often, followed the second or subsequent injections.

In the event of overdosage, not infrequently there was a reproduction of symptoms, such as headache, which simulated in detail those for which the patient sought treatment. Reduction of the dosage usually obviated such symptoms and produced the desired clinical effect. An occasional patient, who had obtained a beneficial therapeutic effect from a certain dose, may at approximately the fourth or sixth administration develop a systemic reaction following that same dosage; however, the desired therapeutic effect can be re-established by reducing the dosage by 25 to 50 per cent.

Most patients could be maintained on a therapeutic dosage of from 1 to

5 gamma, given at intervals varying from three to seven or more days. In children, it was noted that relief tended to last for a longer period of time than it did in adults.

### INTRACUTANEOUS ADMINISTRATION

Most of the patients in this series have, at times, received Pyromen intracutaneously in dosages approximately the same as those that had proved effective by intravenous administration. Intracutaneous administration has been of particular value in treating children; however, no child under the age of eighteen months has been treated with the drug. Children over eight received adult dosage; in younger children the initial dose was usually 0.5 gamma.

Following intracutaneous administration, there is usually a slight erythema and sensation of heat in the area of injection. In no instance was there necrosis, nor was there activation at the site of a previous intradermal injection when Pyromen was subsequently given intravenously. Care was taken not to use the same site for more than one intracutaneous injection.

### SUBLINGUAL ADMINISTRATION

Results of sublingual administration have been quite satisfactory from a therapeutic standpoint. Dosages were usually 50 per cent higher than those administered intravenously. Occasionally, absence of clinical effects indicated the necessity for a further increase in dosage. Duration of benefit following sublingual administration of the drug varied from two to seven or more days. Patients who administered Pyromen to themselves sublingually usually noted a "wearing off" effect so that they presented themselves, of their own volition, every month or six weeks for booster doses, which were given intravenously or intracutaneously.

The intravenous administration of Pyromen usually produced a prompt systemic response and clinical improvement. The response to intracutaneous administration was somewhat delayed as compared to the intravenous route. As one would expect, sublingual therapy was found to produce its effects still later, or in about twelve hours after administration; in a few instances, however, response was quite prompt.

### CASE REPORTS

*Case 1.*—Mrs. H. H., instructress of nurses, aged thirty-six. Headaches; perennial rhinitis; gastrointestinal food allergy characterized by abdominal distress and gaseousness relieved by vomiting; extreme fatigue which was more severe on arising; mental dullness, lethargy and lack of ambition; muscular aching, especially in the nuchal region, thighs, low back and, occasionally, the arms. Proved sensitive to wheat, corn, eggs, white potato and coffee. Inhalant studies showed sensitivity to house dust. Dietary elimination of the above foods and dust injections gave relief of symptoms, but she disliked her diet and lost weight.

A 3-gamma dose of Pyromen intravenously was followed in a few hours by mild symptoms of muscle aching and chilliness. A 4-gamma dose was given four days later without systemic reaction; shortly after the injection the patient experienced

a sensation of increased vigor and vitality and a state of mind suggestive of mild euphoria. A 5-gamma dose, given seven days after the second dose, resulted in moderate chilliness and reproduction of the symptoms of fatigue and headache for a twenty-four-hour period.

Subsequently, 4-gamma doses and dust injections were given at weekly intervals. She was much more alert and ambitious, her appetite increased even though the diet was unchanged, and there was a dramatic increase in her sense of well-being. Subsequently, each of the known food reactors was reintroduced into the diet at intervals of two to four days; large feedings were given without the reproduction of allergic symptoms.

After the fifth intravenous injection of Pyromen the patient was allowed to administer 6-gamma doses to herself sublingually every four to five days, with continuing satisfactory results. She voluntarily returned at four- to six-week intervals for a "booster shot" of 4 gamma given intravenously. She gained weight and continued to eat known food allergens at two- to four-day intervals. Six months later, however, she stated that her allergic symptoms had returned despite Pyromen therapy. A check of her food diary revealed that for some time before the return of symptoms she had been ingesting wheat, corn, milk, eggs, and coffee as often as once or twice daily.

Re-establishment of properly spaced feedings of these foods, along with Pyromen therapy, resulted in complete relief of symptoms and return of her sense of well-being, but oft-repeated ingestion of these foods reproduced her symptoms. She continued rotation of her diet, and nine months after Pyromen was started she was able to discontinue all therapy—Pyromen, dust injections, and all other medication—as long as she was careful not to eat the offending foods at too frequent intervals.

*Case 2.*—Mrs. R. E., a housewife, aged thirty-six. Severe headaches associated with nuchal myalgia; gastrointestinal food allergy characterized by gaseousness, bloating, and occasional diarrhea; perennial rhinitis. Proved sensitive to wheat, corn, eggs, milk, lettuce, tomato, barley, chocolate, orange, and cabbage. Significant inhalant sensitivities to feathers, orris root, house dust, and Alternaria. Titration to house dust and Alternaria and the complete avoidance of feathers, orris root, and the offending foods resulted in almost complete relief of symptoms. Certain minor food reactors such as pork were included in the diet as occasional feedings.

Pyromen was given because the diet was difficult and the patient discouraged. A 3.5-gamma intravenous dose gave no immediate systemic reaction, but twenty-four hours later she felt generalized muscle aching and chilliness. Three days later a 4-gamma dose gave no systemic reaction. Following this dose, the patient was able to add eggs and milk to the diet once daily. Clinical improvement extended for one week, when a 3.5 gamma dose reproduced certain of the symptoms that had been previously noted after ingestion of known food reactors. She was then placed on 4 gamma sublingually every other day and 2.5 gamma intravenously once monthly. At present this patient is able to tolerate spaced feedings of all previously known food reactors except tomatoes and corn.

*Case 3.*—Mrs. M. K., a housewife, aged forty-five. Severe headaches; perennial nasal obstruction with rhinorrhea of thirty years' duration; abdominal cramps, marked distention, constipation, periodic attacks of nausea and vomiting; chronic fatigue not relieved by rest; periorbital edema, edema of the hands and feet. Sensitive to wheat, corn, eggs, broccoli, shrimp, coffee, all legumes except peas, citrus fruits, onions, and garlic, as well as the inhalants: dust, orris root, silk, and Alternaria. Injection therapy for dust, silk, and orris root and avoidance of the food allergens gave almost complete relief for six months. At this time a mild recurrence of all symptoms developed despite continuing inhalant therapy and complete

avoidance of the known food reactors. She was found to have developed a sensitivity to white potato, which was eliminated from the diet with some relief.

Intravenous Pyromen was then given as follows: 3.5 gamma, no systemic reaction, relief of remaining abdominal symptoms, and a sensation of well being; forty-eight hours later, 4.5 gamma, no systemic reaction, felt very energetic and "as if given some sort of mental boost," able to tolerate small quantities of corn oil and white potato. After the second dose a distinct diuresis, coincident with relief of her symptoms, was noted. One week later, 5.5 gamma resulted in slight chilliness and nausea; one week later, 4,5 gamma: chill, slight fever, nausea and severe muscle aching; one week later, 2.5 gamma: chills, fever, myalgia, moderate diuresis, and sensation of extreme hunger.

Therapy was then changed to 3 gamma sublingually, given at weekly intervals for two months. Although minor food allergens were tolerated, major food allergens could not be added to the diet without some reaction. The reactions were less severe and of shorter duration, however, than when not taking Pyromen. Administration was then changed to 2.5 gamma given intracutaneously at weekly intervals for one month, at which time a moderately severe reaction occurred, associated with acute symptoms of a left-sided scalenus anticus syndrome. Pyromen was discontinued for a month; then weekly 2-gamma intravenous doses were given, resulting in no untoward reactions and producing the desirable effects of the original administrations. While it never became possible for this patient to consume the major food allergens in quantity without some reaction, she stated that Pyromen therapy made her "feel more like living, more enthusiastic and able to do things."

Pyromen therapy was continued for approximately thirteen months, with the patient's condition remaining about the same, then discontinued. Two months later she went on a "food binge" and developed a severe reaction which lasted several days, followed by milder, yet constant, symptoms. Pyromen was administered intravenously at forty-eight-hour intervals in doses of 2.5, 3.5 and 4.5 gamma. The third dose resulted in a mild systemic reaction. Subsequently, she has been given 4-gamma intravenous doses at weekly intervals and has been maintained comfortably, though on her original allergic diet. She is now able to tolerate occasional slips in the diet with but mild reactions.

*Case 4.*—Mrs. N. M., food factory worker, aged nineteen. Periodic headaches; extreme fatigue most pronounced on arising; vague gastrointestinal distress following ingestion of certain foods; periodic attacks of antecubital eczema.

Because this patient was of the type that neither could nor would co-operate in dietary studies, it was decided to place her on Pyromen therapy without attempting to determine the specific allergies causing the symptoms. A 2.5-gamma intracutaneous dose resulted in mild muscle aching and chilliness in twelve hours, increase in vigor, dramatic relief of symptoms of chronic fatigue, and increase in appetite. A 3-gamma dose administered three days later gave almost complete relief of headaches, fatigue, eczema, and gastrointestinal symptoms. She was continued at this dosage level, administered once weekly, for three months, during which time she remained symptom free and her weight increased from 99 to 114 pounds.

*Case 5.*—Mr. M. H., engineer. Mild fatigue; mild headaches of recently increased intensity; mild gaseousness and fullness following ingestion of pork and tomatoes. Although a complete physical examination and laboratory studies were made, the patient's symptoms were of such a mild degree that a complete allergic study was not deemed advisable or practical.

A 3-gamma intravenous dose of Pyromen resulted in mild chilliness and muscle aching, relief of fatigue and gastrointestinal symptoms, and marked increase in vigor and ability to carry on daily work. A second 3-gamma dose given four days later

gave similar effects. Subsequently, weekly 4-gamma intravenous doses were given for one month, after which treatment was discontinued. During the six-months' period since therapy was discontinued, he has remained symptom free.

## DISCUSSION

Pyromen therapy gave a favorable response, with relief of symptoms, in a majority of the 125 patients in this series. The most strikingly beneficial results were noted in those patients exhibiting symptoms of allergic fatigue or allergic toxemia. Most patients experienced a sense of well-being, alertness, attentiveness, and increased ability to concentrate. Many patients also experienced a sensation of added vigor and increased ambition. The ability to tolerate foods previously proven to cause bronchial asthma, coughing, nasal allergy, urticaria, atopic dermatitis, headache, myalgia, and various manifestations of gastrointestinal allergy, has been noted in many patients. Others experienced relief of symptoms caused by slips in their diets or relief from symptoms caused by minor reactors still included in their diets. Many patients were free from symptoms after adding foods that had previously caused reactions.

Not uncommonly, patients experienced increased appetite and zest for eating while still on restricted diets. These patients gained weight and, for this reason, the drug was helpful in alleviating their concern regarding dietary restrictions. This observation was noted in a number of instances, and Pyromen is believed to have helped in maintaining such patients under allergic management.

It has been observed that the drug appears to be more effective in the treatment of food allergy than in inhalant allergy. Consequently, inhalant therapy was continued in conjunction with administration of the drug.

Patients in whom Pyromen therapy has been carried out without careful diagnosis of food allergies will occasionally respond dramatically, but these are the exception rather than the rule. It is important, therefore, in all patients except those with minor symptoms, to diagnose the allergy before Pyromen therapy is started. If this is done, foods may be added to the diet, first at spaced intervals then more frequently, to test the efficacy of the drug in protecting against allergic reactions. More patients will be seen who obtain the blocking effect of Pyromen to some of their major (Case 2) or minor (Case 3) food reactors than will those who respond with dramatic relief of symptoms to all food reactors (Case 1).

In the treatment of minor food allergies (Cases 4 and 5) such as acute urticaria, mild headache, mild fatigue, or mild gostrointestinal symptoms, Pyromen alone, without other therapeutic measures, was generally effective. We do not, however, recommend therapy without a careful history and physical examination, and the necessary laboratory and x-ray studies to rule out organic disease other than allergy.

Of clinical interest is the occasional diuresis concurrent with clinical improvement, such as was noted in Case 3. This observation has been noted in two other patients in this series. Each of these patients presented peri-

orbital edema and puffiness of the hands and feet as part of their original complaints.

Not all of our cases have responded favorably to Pyromen therapy. Why one patient will respond satifactorily while another with the same symptoms will not respond, is a matter that has not been determined. It is felt, however, that the proper dosage and frequency of administration of Pyromen has not been definitely established. It is suspected that some failures might have responded favorably had they received smaller or larger initial doses or more frequent administrations of the drug. There has been an occasional case in which excellent therapeutic results were obtained following the initial doses, only to have this effect wear off in spite of both raising and lowering the dosage. This phenomenon cannot be explained at this time, but it is believed that it, too, might be a question of proper dosage and frequency of administration.

## SUMMARY AND CONCLUSIONS

1. Pyromen is a nonprotein, nonanaphylactogenic bacterial substance which produces a generalized stimulation of the reticuloendothelial system.

2. A series of 125 patients with food allergy, with or without inhalant allergy, was treated with relatively low doses of Pyromen for periods of time varying from one to seventeen months; representative cases are reported, describing dosage schedules and clinical responses.

3. Pyromen therapy gave a favorable response, with relief of symptoms, in a majority of the patients in the series. Best results were obtained in those patients in whom a specific diagnosis was made and the allergy partially controlled before Pyromen therapy was instituted.

4. Pyromen therapy has proven to be a most valuable aid in the management of food allergy where the diet is cumbersome and morale is low, and has been helpful in maintaining such patients under allergic management. It has increased food tolerance in some of these patients; in others it has improved morale and sense of well-being, although no allergenic foods could be "re-added" to the diet. It has decreased the severity of reactions in patients making dietary slips and has made it possible for certain severely allergic patients to occasionally enjoy a general diet.

5. As our knowledge of dosage technique increases, we may expect further improvement in the clinical results obtained.

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*1206 Security Tower*

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## ALLERGENIC EXTRACT VIAL SEALS

Cellulose bands for sealing vials are made of pure cellulose extracted from wood pulp. In its raw form, this is called viscose and is regenerated by coagulation. Both transparent and opaque bands are made. Numbers, letters, or names of various allergens could be incorporated into the seals. After molding and cutting, the bands are stored in wet form in a preserving fluid consisting of approximately 8 per cent CP glycerine as a plasticizer with a trace of formaldehyde, a trace of other harmless preservative, and distilled water.

These seals may be made in any width and diameter. To seal a vial, all that is necessary is to slip the damp band over the rubber stopper so that the mid-point of the band is at the junction of the rubber stopper and the glass vial. Vials may be first sterilized and capped, then banded, and after a few hours they are available when needed, unquestionably sterile. Assuming complete sterilization and caps without holes, this sterility may be maintained for years. The bands shrink on drying, and the seal made between the rubber cap and the glass is so tight that it is usually impossible to remove the cap without cutting or breaking the band.

The seals are made in various sizes, expressed as 32 x 30, where 32 is the widest diameter over which the band is to be applied and 30 is the length, both expressed in millimeters.

Prices decline as larger quantities are ordered. If allergists in their offices and clinics would use standard-sized vials such as the 12 cc capacity vial, it would make for uniformity and sterility. The American College of Allergists could order these bands from a manufacturer and then resell them in smaller quantities to members as needed.

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# PYROMEN IN THE TREATMENT OF PERENNIAL RESPIRATORY ALLERGIES

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THE pharmacology of Pyromen® has been carefully studied for the past several years.[1,15,16,17] Clinical investigations[3,4,5,6,14,18] of Pyromen have shown that it may be administered safely with a wide variance of dosage.

On injection of Pyromen intravenously in man there is an initial leukopenia, with a subsequent leukocytosis consisting principally of myeloid elements developing in the presence of a sustained lymphopenia and eosinopenia.[8] It has also been shown that the experimental ingestion of an allergenic food,[7,10] or drugs[9] is followed by a similar blood response as well as following the administration of adrenocorticotropic hormone (ACTH) in humans.[2,11,13] The effect of ACTH in the treatment of allergic diseases suggests that Pyromen may be of use in allergic states.

Those first employing Pyromen in the treatment of allergic diseases used large intravenous doses with the object of producing high fever. It soon became evident that relatively small doses which were not followed by any marked constitutional symptoms gave better results.

In the present series, fifty patients with perennial respiratory allergy have been treated during the past five months. Some patients have been on maintenance dosage since this time, while more recent patients have been under treatment for only about three weeks. The procedure of Randolph and Rollins[12] of using subfebrile doses was employed throughout. This has consisted of an initial intravenous dose, 0.5, 1.0 and 2.0 gamma on three consecutive days. This was followed by 2 gamma three times a week for two weeks. Subsequent doses just below the reaction threshold were given at intervals which maintained the patients more symptom free. The majority showed improvement with one or two administrations per week of one third to one half the previous maintenance dose. There was considerable variability in clinical response[12] so that the dosage schedule may range from 0.5 to as high as 15 or more gamma.

In the chronic mixed type of perennial asthma patients with a superimposed chronic infection, an increase of each succeeding dose by 50 per cent until improvement was noted was found to be a safe and satisfactory procedure. A maintenance dose was usually somewhat less than that noted from the initial therapeutic response. Children usually obtained relief for a longer period of time than adults.

Many cases of severe perennial respiratory allergy are encountered in the middle and Pacific northwest. The sudden and extreme changes of temperature and humidity often result in a superimposed chronic infective sinusitis and bronchitis on a pre-existing upper and lower respiratory al-

Approved for publication June 22, 1951.

lergy. These cases are most refractory to the usual elimination, avoidance and immunization measures. Pyromen was first resorted to in the treatment of these patients when every effort towards their management by the usual procedures was unsatisfactory. If any relief could be obtained by some other procedure, its use was thought justifiable.

The majority of the patients received Pyromen intravenously. Recently, however, some were treated sublingually. Since Pyromen is absorbed through the buccal mucosa, 5 gamma per cubic centimeter of saline solution was allowed to remain in contact with the buccal mucosa for at least five minutes before swallowing. There was a less marked variation in the cellular elements than when Pyromen was administered intravenously. The oral administration delayed the onset and severity of constitutional reactions compared with that of the intravenous route. The results were so variable, however, that the method was abandoned except when used in several children combined with occasional intravenous therapy. Oral therapy seemed to maintain clinical improvement initiated by previous (three or four) intravenous injections. It is interesting that even on the initial dose of 0.5 gamma an occasional patient would respond quickly with mild constitutional reactions consisting of fatigue, irritability and listlessness, whereas others could tolerate comparatively much higher doses without any untoward reactions. Not recognizing that the schedule of dosage requires considerable individualization may be responsible for the reported failures in the use of Pyromen. Small doses intravenously at comparatively infrequent intervals, or at intervals just sufficient to show continued clinical improvement, gave the most satisfactory results.

A few case reports are presented which illustrate the negative as well as the positive results.

*Case 1.*—D. W., a man aged forty-six, was referred by Doctors Harriet and Frederick Judy of Spokane. Briefly, he consulted them first on November 1, 1948. His first allergic manifestations occurred in 1940, when he had hay fever. In 1942, a physician removed a large number of nasal polyps. Almost immediately afterwards severe asthma began. He was tested by a competent allergist and was placed upon a desensitization routine with little or no results. Since 1942 he has moved to various places in the southwest, including Mexico. His last serious hospitalization was in Tucson, Arizona, in 1948 prior to moving to Spokane. At that time he was taking Benadryl, "with no effect"; Pyribenzamine, with "a little help"; Demerol, "useful to go to sleep"; Novalene tablets, "no good at all"; and aminophylline tablets, "do help."

He had pneumonia four times in 1946. At the time he consulted the Doctors Judy he had a productive cough and sinusitis; he was taking a cold vaccine. Eating of corn, milk, peanuts or watermelon caused increased respiratory symptoms. He was markedly underweight. There was frontal and maxillary sinusitis. There was some wheezing and râles. The heart was regular in rate and rhythm with no murmurs. X-rays revealed heavy peribronchial markings with a few calcified lesions. The heart was of the small, long, asthenic type.

The patient was rather reluctant to undertake any new drug therapy or to continue immunization measures. He had tried, in turn, Isuprel, Orthoxine, and Pyribenzamine, as well as Norisodrine, with little or no beneficial effect.

On January 5, 1950, he developed status asthmaticus and was hospitalized. He received the usual therapeutic treatment for this condition. Aminophylline, epinephrine, and Norisodrine all seemed to cause emesis. He lost weight from 126 to 112 pounds. Nethaphyl gave no relief. Another acute attack hospitalized him, but on March 9, 1950, he began definitely to improve with a few doses of aureomycin. He then readily responded to the suggestion that he see a psychiatrist. The psychiatrist was able to determine several areas of conflict in his background but did not make sufficient progress to relieve all the trigger points of his asthma. Since he could not be moved, his blood serum was sent to our laboratory for a series of passive transfer tests.

Blood examination November 1, 1948, showed the blood sedimentation rate normal; the differential count showed 4 per cent eosinophiles, and the white blood count was 11,100. All controls were negative when performing the passive transfer tests. It was found that he was extremely sensitive to farmhouse dust, the atmospheric molds, and hay fever grass pollens native to Washington, as well as western ragweed, sages, pigweed, and English plantain. He received a pollen as well as a dust and mold antigen mixture, with very little benefit.

When seen in consultation with the Doctors Judy, he was extremely emaciated, could not lie down, and was in apparent continuous intractable asthma. He had been started also on ACTH in February, and he stated that he did not seem to be feeling any different from when he was not taking it. He was receiving small doses, and it was suggested that he start on a 25 mg schedule. The patient developed severe asthma symptoms about an hour after the administration of ACTH. Cortisone was then used with similar effects. Finally, on February 16, Pyromen therapy was initiated in subfebrile doses, of the magnitude of 0.5, 1.0, gamma. He then became worse after three or four injections, and on February 18 he was again hospitalized for acute asthma, and despite heroic measures, expired on February 19, 1951.

*Case 2.*—G. L. H., a man, aged fifty-eight, noted his first attack of asthma in 1919, following an attack of sinusitis, but this did not become severe until 1927, when he had paroxysms of coughing. Since that time he has had continuous wheezing with occasional paroxysms throughout the year but with no seasonal variations. He obtained some relief in the dry southwest climate. Sulfonamides relieved him. X-ray therapy gave him some relief, but his chronic asthma persisted. He obtained a severe reaction from penicillin by aerosol. Antihistamines aggravated his condition. He visited a well-known clinic and was found quite sensitive to house dust. Injection treatment with a bacterial vaccine made from a culture of his sinuses gave considerable relief. A radical operation was also performed on the right antrum.

When he was examined on June 29, 1949, there was a marked cloudiness of both antra. Smears from the right antrum showed 100 per cent eosinophiles. Cultures revealed Gram-negative staphylococci and *M. catarrhalis.* There was considerable emphysema, with diaphragmatic adhesions, and bilateral sibilant râles. A differential blood count revealed a 9 per cent eosinophilia.

Intradermal tests, followed by individual food tests, revealed that there was little or no sensitivity to foods except to chocolate and fruits. A prescribed diet gave no relief. Immunization measures gave some relief, but the patient continued with considerable coughing and wheezing.

During the first week in April, Pyromen was administered intravenously, and after nine injections the patient was markedly relieved. At the present time he is on a maintenance dose of Pyromen, 4 gamma.

*Case 3.*—W. F. P., a man, aged sixty-five. The diagnosis was perennial bronchial asthma. He was first seen on December 19, 1950, with chronic asthma interrupted by severe paroxysms and profuse expectoration. The onset was in July, 1949, with

sinusitis. Following a polypectomy, he developed a cough which was followed by asthma. Nasal symptoms consisted of a chronic mucopurulent discharge and nasal blockage. He was markedly sensitive to codeine and antihistamines, to all of which he reacted unfavorably. When he was hospitalized for ten days and placed on ACTH, he was quite free from symptoms for two weeks; then asthma attacks returned, and ACTH no longer helped him. The skin tests for foods, augmented by individual food tests, were practically negative. He was quite sensitive to house dust. Repeated blood examinations revealed a leukocyte count ranging from 12 to 14,000. Pyromen intravenously was started January 15, 1951, when he received 0.5 gamma. On January 16 he received 1.0 gamma. Following this he developed an asthma attack, and the dosage was reduced again to 0.5; subsequently he showed a gradual satisfactory improvement.

This patient showed a marked response to a very small dose of Pyromen, and illustrates the extreme variability of the dosage necessary for results. Successful treatment depends upon an appreciation of this variability.

*Case 4.*—Mrs. M. S., aged fifty-four, a housewife, was first seen on December 7, 1949. The diagnosis was perennial asthma and seasonal hay fever due to tree, grass, and weed pollens. The onset of asthma with cough, nasal discharge, anosmia and agustia was in 1948. Cold weather aggravates her asthma. She was found definitely sensitive to certain foods and to atmospheric molds, but her chief inhalant offender was house dust. She was subject to frequent respiratory infections. A sojourn in Arizona did not give her any relief. She has been on immunization injections, and on a prescribed diet and various sympathomimetic amines with some relief. Her case is typical of the chronic cases frequently encountered in this region.

On January 2, 0.5 gamma of Pyromen was given intravenously; on January 3, 0.1, and January 4, 2 gamma. It was found that subsequently 0.2 was her maintenance dose. A dose greater than this produced flushing and fatigue. On the maintenance dose of 2 gamma she improved steadily, developed a sense of well-being, and was able to eat certain offending foods. To date she has had very satisfactory results.

*Case 5.*—R. S., a man, aged fifty-six. The first diagnosis was perennial bronchial asthma. The onset was in 1947. He was hospitalized for an acute attack at that time and received a series of skin tests. He had some perennial nasal allergy. He had a submucous resection and polypectomy in 1947. After continued use epinephrine failed to abort the attacks. He was found slightly sensitive to foods, and his leukocytes were continuously elevated. Immunization measures, as well as all medication tried, were only partly successful, and the patient was never free from asthma.

On January 3 he received 0.5 gamma of Pyromen intravenously, and it was found that his maintenance dose was 2 gamma. After the fifth intravenous injection of 2 gamma of Pyromen his attacks commenced to get less severe, and by January 17 he had no paroxysms and could carry on his normal duties. Recently he has been receiving only 1 gamma, and has been entirely free from attacks.

*Case 6.*—Mrs. O. R. S., aged fifty-eight. The diagnosis was perennial bronchial asthma. The duration was ten years, with an insidious onset. As soon as cold weather sets in she is troubled with sinusitis. She had no relief in California. She had severe attacks of recurrent asthma during the winter of 1949. The paroxysms were severe. She was unable to lie down for three weeks. During the past ten years she has had numerous polypectomies. Based on the tests of another allergist, she was placed on an elimination diet for two years without any appreciable improvement. She was not found sensitive to foods but was sensitive to house dust, mattress linters, and atmospheric molds. In November, 1950, she developed a very severe chest cold and went into status asthmaticus. During the winter frequent tests revealed a leukocyte

count averaging 12,000 to 14,000. The x-ray revealed a marked peribronchial infiltration, and considerable emphysema. Frequent blood-pressure tests indicated an essential hypertension averaging 170/110.

This case is cited because of the desire to learn the effect of Pyromen on a patient with hypertension. The electrocardiogram was normal.

On January 8, 1951, she received 0.5 gamma without reaction. A dose of 1 gamma produced a slight temperature followed by a severe attack. The dosage was not reduced, however, and on January 15, 2 gamma was repeated and her breathing became much easier. On January 19, 2 gamma was given, followed by a slight attack. Again on January 22, when the same dose was repeated, she developed a temperature of 100° and had considerable wheezing. Then 1 gamma was administered twice a week, and there was considerable improvement. Although chronic asthmatic patients require relatively larger doses than those sensitive to foods, she has been relatively free from any attacks, although with a maintenance dose of 1 gamma she has some wheezing on exertion. Blood pressure observations during this time showed no appreciable elevation. Since large doses were not given, there was no opportunity for observing the effect of the supposed pituitary-adrenal stimulation expected with higher dosage.

## DISCUSSION

Pyromen was employed in fifty patients suffering from perennial asthma. An older group, the majority of cases also being complicated by a superimposed infection, was selected for this study. All of the patients had received a thorough allergy study and management by orthodox procedures. Practically all were receiving immunization injections and, where foods were proved to be also a factor, were on a prescribed diet eliminating known offenders as much as possible.

Since it has been the experience of others[12] that Pyromen therapy is not as effective in controlling symptoms caused by inhalants as those caused by food sensitivity, it has also been observed that if specific inhalant therapy is combined with Pyromen treatment the results are better than if either is used alone. Logically these chronic cases of perennial respiratory allergy would be a more rigid test of the effectiveness of Pyromen than heretofore observed, and if any benefits were derived from supplementary treatment with Pyromen the procedure was justified.

Complications were relatively few. A few patients with myocardial damage developed transient ectopic beats immediately following intravenous Pyromen. A large percentage of these chronic patients had complained of undue fatigue. It was noted that the majority lost their fatigue and had a feeling of well-being when under treatment with Pyromen.

Of this small series of fifty, twelve patients received good results. All were having frequent severe attacks of asthma despite specific inhalant immunization and food management. They have suffered no more severe paroxysms since receiving Pyromen therapy. Occasionally one will develop considerable asthma which can be controlled by other drugs, particularly antibiotics, when the attack is caused by an acute respiratory infection. They rest comfortably at night, something which none of them did before the supplemental Pyromen treatment. With limited efforts they have been

able to carry on their daily work, have regained confidence, and have lost the fear of impending attacks.

Eighteen patients obtained considerable relief characterized by lessening of the frequency and severity of the attacks, with partial loss of their marked fatigue, and seemed to respond more readily to the usual drugs used as bronchial dilators and vasoconstrictors. Those whose condition was improved by Pyromen seemed to obtain more prolonged and greater relief from subsequent doses following the initial injection. Twenty of the patients received little or no appreciable benefits.

Two of the patients with good results, who showed adrenaline insufficiency, were given two weeks' treatment, preliminary to Pyromen therapy, with intramuscular injections three times weekly of 1 cc Lipo-Adrenal Cortex (Upjohn).

Considering that the majority of these patients were potential chronic intractable cases of asthma, trial treatment with Pyromen intravenously appears to be justified as an adjuvant type of therapy in these distressing cases.

## SUMMARY

In a preliminary report of fifty patients with perennial respiratory allergy treated with Pyromen, it was found to be a definite aid in some cases, especially when combined with specific allergic diagnosis and therapy. Beneficial results are slower than those following ACTH or cortisone therapy, but the relatively few ill effects compared with those from ACTH and cortisone would warrant its further trial. Subfebrile intravenous doses ranging from 0.5 to 15.0 gamma (or micrograms) are recommended.

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# THE GENESIS AND TREATMENT OF A RECURRENT ATTACK OF ASTHMA

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SOME years ago it became apparent that the clinical manifestations of allergy could not always be understood on the basis of the classical concepts of either immunologic allergy, its complications, or its sequelae alone. With others, we turned for better understanding to the field of psychosomatic medicine. It was for this reason that Kenneth, a seven-year-old asthmatic patient, was recommended for psychotherapy.

As an allergist, I (H. M.) had been taking care of Kenneth for well over a year. He had had asthma since the age of three. On the basis of his many definite positive skin reactions, I had attempted to protect him against the assaults of the allergens which I felt were the cause of his asthma. Despite this, there was practically no diminution in the severity or persistence of his clinical symptoms. He had severe attacks of asthma practically every night and wheezed a good part of each day.

Cathy, Kenneth's mother, described him as a good child. In contrast to his younger brother who was not allergic, Kenneth's behavior was quiet, unhostile, and unaggressive.

During the many months when Kenneth had come in once or twice a week for injections he seldom spoke. He never complained. He passively offered his arm each time and then hurried from the room. His hurrying from the room in the face of his passivity and wordlessness made me feel that he hurried out as though not to be caught expressing his dislike of the pain and his anger at the doctor who had caused it.

Despite my repeated suggestions that Kenneth's asthma might have an emotional component and that he should have play therapy, Kenneth's mother hesitated to follow my recommendation until he began to fail in his school work. The school failure touched off considerable anxiety in her, and she agreed not only to Kenneth's having play therapy but also to having psychotherapy for herself, the treatment of a parent being a necessary part of the treatment of a child. Eventually the father also came into group therapy.

After a year and a half of psychotherapy twice a week, Kenneth would go for two or three weeks or occasionally for a month without asthma, and then the attacks were much less severe. His physical improvement was accompanied by marked improvement in his personality and by elevation in his school standing to above average. Meanwhile, with both parents and the child in psychotherapy, it was possible to gain deep insight into

Presented at the Seventh Annual Congress of the American College of Allergists, February 11-14, 1951, Chicago, Illinois.
Approved for publication April 25, 1951.

tional dynamics. Furthermore, it was often possible to trace an attack to events and emotional interplay between family members and to see as well some the fantasies that were activated in the child's mind and the part that these played in an asthmatic episode. Some of these I will try to show you now, and to show you also some of the things that were done with the child in psychotherapy.

For one thing, the dynamics connected with the beginning of his asthma were brought into focus. Kenneth's mother and father were having difficulty in their marriage, and Kenneth's mother, Cathy, had not wanted children, but if she *had* to have them she preferred that they be girls.

During his infancy Kenneth had had some eczema, but it was not until his mother's second pregnancy that his asthma began. Describing this pregnancy the mother stated, "I went through nine months of hell. Even inanimate objects became possessed of the devil. Kenneth was into everything, so I put him into a room and left him there in spite of all his calling . . . and when he kept on asking, 'Will the new baby be a brother?' I thought I'd go mad, and one day I screamed at him, 'No. No. No. Not another boy.' "

Thus Cathy had rejected Kenneth not only as a person but also as a boy. As with many other asthmatic children he felt outcast and lonesome, hungry for love and unable to express the hostility that became manifest in his play after he found that he could trust the therapist. (D.W.B.)

He sought comfort and acceptance and belated satisfaction for his hunger for affection by sitting on the therapist's lap session after session, sucking a nursing bottle despite his seven years.

He had a dream of going to a picnic ground. He looked around for something to eat. But in vain. All the tables were empty. There was no food.

When Kenneth was asked what he thought of the dream, his answer came quickly. "The mother was too busy fighting with the father to feed the children." Thus he recognized his rejection and expressed his hunger for affection.

Repeatedly he showed his fear that his mother might leave him. Repeatedly he showed in his play that he was angry at his parents, but as so many asthmatic children, he blocked it, he was unable to give outward indication of his anger; instead he turned it on himself and wheezed. Repeatedly—right in the sessions—when he was able to bring out his anger, the wheezing would cease. But he was so full of an unnamed fear that often he did not dare to bring out the anger.

Gradually it became apparent that Kenneth had not only felt rejected as a hungry baby or child, afraid that his mother would not feed him, but that he had also felt his mother's rejection of him as a male. He played out a drama he improvised with a clay boy representing himself. He said, "He's an unhappy boy. He wants to be happy. He keeps

wondering how. He's a sock-eyed kid. See him; how ugly! Mothers don't like ugly boys."

As a boy he lived in constant fear of injury. He showed this again and again in his sessions. He played with the sock-eyed replica of himself, as example, and said, "I'm making him walk now. Booms! There he trips. His head is almost off. His arms are almost off and one of them got much too short. He has to go to bed and stay there and his mother has to feed him now at least once every day. He's happy at last. His worries are gone."

Thus, by being hurt or sick he could in fantasy get his mother. But being a boy was still dangerous.

In another session he related, "Hamburger, my dog, had a girl dog come to see him. Hamburger got all excited." Kenneth's own excitement was apparent.

"And so did you," the therapist added.

He nodded. Then stopped short.

Suddenly worried, he questioned, "Tell me, why do they cut dog's tails off?"

Here, as in other sessions, he showed that the idea of excitement, his own excitement, not only Hamburger's, had, for one thing, brought the idea of injury in its wake. This he went on to tie in with his own excitement when he masturbated and the fear of being punished for his badness, as he expressed it, by having his own tail cut off.

He came in very tight to the following session, wheezing perceptibly. "Did you know," he said, "that mother guppies eat up their babies?" He was obviously very frightened.

He wanted again to climb onto the therapist's lap. Once there, he seemed to feel safer and was able to go on. "Yes, mother guppies eat their babies when they should love them and let them get close like they want to. And yesterday, do you know what happened? My mother was cleaning the tank and she caught a baby guppy in the tube of the cleaner."

Anger came up into his voice and the wheeze vanished. "She should have been more careful. It was a *boy* guppy, too."

Thus the idea of the boy child being close to his mother also carried danger in its wake.

It is interesting to note how his fantasy of his mother's destroying the boy guppy fitted in with his mother's fantasies of destroying a male.

Later the same day she came in and talked of her husband, Vic, who had recently lost his job. She recounted a dream of the night before in which she had attacked a man with her teeth, trying to destroy and devour him in cannabalistic fury.

Into the therapist's mind flashed what Kenneth had told about the mother fish eating the boy guppy. Had Kenneth apprehended what lay in Cathy's unconscious before she herself had perceived it?

Cathy was asked what the dream made her think of.

"Vic's father when he was young. He gave Vic nothing. *My* father gave me nothing either."

All softness went from her voice. "I hate him. I hate all men. Vic, too. He doesn't give me anything. Why did he lose his job? I feel starved and hungry. I want to tear him to pieces. Bite him like the woman did in my dream. Oh, God, I wish I'd never had children. It's too heavy. Too hard."

That night while slicing bread, Cathy severely cut her finger and fainted. When she came to, Kenneth was leaning over her, his face gray with terror, crying, "Don't leave me, Mother. Please, please, mother, please don't die."

It was later that evening that Kenneth went into the worst attack of asthma he had had in the year and a half that he had been in play therapy. In that year and a half the baby and child in him had grown. In that time he had come to realize his need for food, warmth, comforting, and appreciation and to glimpse his own anger over having been deprived of these values. He had also come to see that he needed acceptance not only as an individual but as a male individual. Moreover, the fear of rejection and the anger over it carried connotations also having to do with boy guppies being destroyed, dog's tails being cut, his own tail being cut. The sight of his mother's finger cut and bleeding had suddenly touched off all these dreads and had rekindled anger, as became apparent in what ensued. But the fear and anger could not yet come out clearly in this characteristically blocked allergic child. He had not yet worked sufficiently on them. So the asthma persisted, a physical expression of the emotional conflict going on within. For a week he wheezed violently day and night. All the medication was of no avail.

Since Kenneth could not come into the office at the end of this week of ineffectual medical treatment, the therapist (D.W.B.) finally went to his home. Much of what follows is from her notes, which she routinely took at each therapeutic session.

Kenneth was sitting up in bed, propping himself on the flat palms of his hands behind him, huddling forward, his chest heaving, his shoulders hunched up, his pupils wide as in fear.

The therapist sat for a little while quietly with him and then, knowing that he couldn't, she started to talk. She told him that she knew his mother had cut her finger and he'd seen her faint. She wondered if the blood, perhaps, reminded him of things he'd been talking about, such as dog's tails being cut off. He nodded with a look of relief, so she went on, "It made you afraid of a lot of things, didn't it? Of other things that might get hurt and cut? On you, maybe? Because of things you've done that you thought were bad?"—referring to his fear of reprisal over masturbation.

He lay back and after a few minutes he put out his hand and touched

hers and whispered, "You won't send me away!"—the touch expressing his longing for affection, and his words the fear of his anger and of losing his mother that the thought of her dying had reactivated.

Then through his wheezing he whined, "Hamburger, my dog, barks all night. Poor little dog. He's shut out and lonesome. He's neglected." He paused a moment and then, gathering strength, he announced, "He's mad. When Hamburger is put to bed tonight, he will want to get up and bite all the people who shut him out. Dogs are just like people, mad."

With this oblique acknowledgment of his own anger which he had had so much difficulty in expressing outwardly, his wheezing lessened. And then, unbelievably, he laughed.

"Dogs are so funny. They come in and they shove their funny black noses—the little, round wet tip of their noses—right into your ear. Just like people, they want to get in. They want to go in and shove the husbands and brothers out and be inside the mother and be the onliest one."

The therapist nodded and said, "Just like a lot of children do, too. They want to be inside the mother and be the onliest one."

He looked reassured. "Yes, they do!"

"But," the therapist added, "they don't have to get their tails cut off for that. And they don't have to get sent away."

"No, they don't." He sighed and took a deep breath. The yearning was expressed, the fear was allayed, and Kenneth's anger had come out in the open. And now the wheezing was gone.

Kenneth went on in psychotherapy for a year longer, making a total of two and a half years. He was followed for three years longer, coming in for occasional sessions at his own request. During the last eight months of his therapy and the subsequent period of the three years of follow-up, Kenneth had only two very mild attacks of asthma, despite several occurrences in his family which subjected him to severe emotional strain.

If life grew too hard or too heavy, Kenneth might always retreat into asthma. That had been the pattern laid down by the fact that his constitution had furnished him with this potential for refuge, escape, and the expression of anger. But because of the understanding he had of himself and of his own feelings, it would take much more to upset him. He no longer needed to flee from feelings he had formerly blocked because they made him too guilty and anxious. He could bring these out now into the open, rather than disguise them in asthma.

This he expressed in his own words. "I think I can manage . . . I don't have to hide from myself any more that my father and mother get me mad . . .

"Mother keeps making everything bigger. Father keeps making everything smaller. But as for me, things are more according to size. I guess I'm further along than they are because we started with me when I was

*(Continued on Page 557)*

# THE MUSHROOM FLY AS A CAUSE OF BRONCHIAL ASTHMA

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IN 1938, Kern[1] first reported a case of bronchial asthma due to the mushroom fly. This tiny fly, *Aphiochaeta agarici* (Fig. 1), appears in clouds and swarms twice yearly. It is so small that it readily penetrates ordinary sixteen-gauge house screening, getting into one's mouth, nostrils, and even soup. The greatest swarms appear in spring (March, April, and May) but also to a lesser degree in October and early November.

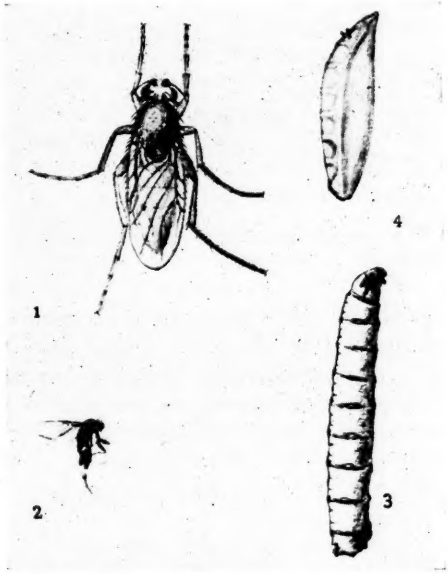


Fig. 1. Phora or manure fly (Aphiochaeta species). (1) Adult fly, dorsal view. (2) Adult, lateral view. (3) Larva, lateral view. (4) Pupa, lateral view. All much enlarged. (From *Pennsylvania State College Bulletin* No. 270, by Mr. C. A. Thomas.)

The larvae, which get into the mushroom beds from the horse manure pile when spring and fall plantings occur, eat out the stems and caps of the growing mushrooms, leave the mushroom houses through doors and ventilators, and descend on the neighborhood in clouds, to annoy everyone and to make certain susceptible people wheeze.

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Presented before the Philadelphia Allergy Society, October 25, 1950.
Approved for publication January 29, 1951.

*Geographic Distribution.*—As can be seen from Figure 2, the mushroom industry is mainly in southern Chester County with Kennett Square as a center and stretching along the Baltimore Pike from Chadds Fork to Oxford. Now, although there have been reactors from other sections of the

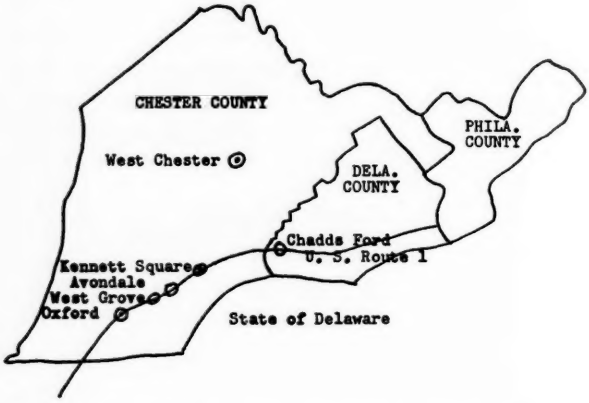


Fig. 2. Counties of southeast Pennsylvania, showing distribution of mushroom fly.

area, all of the patients who had enough clinical allergy to require treatment have come from this section. It might be stated here that although the majority of mushrooms grown in the United are raised here, they are also grown in the suburbs of Chicago, Kansas City, and San Francisco, along the upper Hudson River and at Buffalo, New York. So it can be seen that the subject may have national as well as local interest because mushroom growers assure me that the mushroom fly is found wherever this delicacy is grown.

About 1947 the industry started to use DDT spray to eliminate this and other pests. This has cut down the amount of damage to the mushroom crops, but interestingly enough the adult fly still appears in fairly large numbers in the homes. The only effect it has had on asthma caused by this agent is to make it more difficult to collect enough flies for extract making. The last field trip in May, 1950, required two hours to find a "dirty house" (i.e., one not sprayed) where enough adult flies could be found to make the extract. And now I am told that there is appearing a fly of the same species which is developing immunity to DDT and is no longer destroyed as readily.

In regard to the extract, the live flies are gathered at the height of the season by a special suction device contrived by Mr. C. A. Thomas, Pennsylvania State College entomologist. Coca's extracting fluid is used. Nitrogen determinations have shown values ranging from .38 mg N

per cc to .56 mg N per cc. A value of approximately .005 mg N per cc has been found best for *intradermal testing.* In treatment with this allergen, we start with an extract ten times more dilute than that giving a slight (+1) reaction and build up to tolerance.

TABLE I

| | Jefferson Allergy Clinic (Philadelphia) | Chester County Hospital Clinic (West Chester) |
|---|---|---|
| Total number tested ..... | 50 | 316 |
| Reactors ..... | 0 | 50 |
| % reactors ..... | 0 | 15.8% |
| % of reactors with clinical allergy to fly ..... | 0 | 18% |

It is interesting to see from Table I the geographic distribution of reactors to this allergen. Fifty cases in succession were tested at the allergy Clinic at Jefferson (Philadelphia) with no positive tests. Of the 316 tested at the West Chester Clinic, fifty (15.8 per cent) gave positive intradermal tests. Careful checks revealed only nine of this fifty in whom it was felt that the mushroom fly was an only or partial cause of clinical bronchial asthma. It is noteworthy that each one of the nine dwells in the localized area illustrated in Figure 2 where the fly concentration is high.

Five cases are herein abstracted. These have been treated consistently with the mushroom fly extract since 1946 (four years).

*Case 1.*—Miss L. D., aged forty-five, residence—West Grove.

*Diagnosis.*—Allergic bronchial asthma. Onset at thirty-nine years of age in March.

*Skin reactions.*—Marked: mushroom fly. Moderate: chocolate, orris root, Alternaria, feathers. Slight: mushroom, pork, cabbage, coffee.

*Passive transfer.*—Positive moderately to mushroom fly.

*Treatment.*—Mushroom fly, (1:1000) 0.5 cc and Alternaria, (1:100) 0.5 cc every four weeks for one year; and finally fly, (1:1000) 0.5 cc every four weeks.

*Results.*—No asthma since onset of treatment.

*Case 2.*—Mrs. C. W., aged twenty-nine, residence—Kennett Square.

*Diagnosis.*—Hay fever and asthma. Onset April and May, 1945. Seasonal exacerbations in spring and fall.

*Skin tests.*—Moderate: mushroom fly (1:1000), house dust.

*Passive transfer.*—Markedly positive to fly.

*Treatment.*—Desensitized with fly, (1:100) 0.5 cc every three weeks.

*Results.*—Satisfactory.

*Case 3.*—Mrs. T. DiC., aged forty, residence—Kenneth Square.

*Diagnosis.*—Allergic bronchial asthma with exacerbations in spring and fall. Symptoms aggravated by appearance of mushroom flies.

*Skin tests.*—Marked: corn, mushroom fly. Moderate: house dust. Slight: chocolate, feathers.

*Treatment.*—Mushroom fly (1:100) 1 cc. House dust (1:10) 1 cc. Stock vaccine (1:10) 0.5 cc at three or four week intervals.

*Results.*—Good. Once when mushroom fly extract not available had moderate asthma when flies in the air.

*Case 4.*—Mrs. E. C., aged thirty-six, residence—Kenneth Square.

*Diagnosis.*—Bronchial asthma. Onset winter, 1945-1946. Much worse in April, 1946, with advent of mushroom flies.

*Skin tests.*—Moderate: mushroom fly, house dust, feathers, mushroom. Slight: rice, tobacco, chocolate, and coffee.

*Treatment.*—Perennial to fly, house dust, and stock vaccine.

*Results.*—Asthma-free in general. Occasional wheezing with winter colds in January and February.

*Case 5.*—Mrs. A. C., aged thirty-eight, residence—Kenneth Square.

*Diagnosis.*—Bronchial asthma. Onset fall, 1940. Then free of wheezing until October, 1943, and then on and off until May, 1944. From then (except for occasional wheeze with colds) good until October, 1946, when she had a moderate spell. Recurrence of wheezing in January, 1947, following an acute virus pneumonia. Asthma again in March of 1947 and hospitalized for acute attack in May, 1947.

*Skin tests.*—Marked: mushroom fly. Moderate: house dust, feathers, Monilia, cow dander, peas, spinach, tomato. Slight: kapok, red beet, cabbage.

*Treatment.*—Fly extract, house dust, stock vaccine.

*Course.*—One acute asthmatic attack Christmas, 1948, since above regime.

## CONCLUSIONS

The mushroom fly (*Aphiochaeta agarici*) appears to be a causative factor in the production of bronchial asthma in a given geographic area. It has been practical to make a potent extract of this antigen both for diagnostic skin testing and for treatment. Passive transfer antibodies can be demonstrated. Treatment with ascending doses of the extract seems to be feasible in controlling asthma caused by this agent.

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## THE PRESENT STATUS OF PEDIATRIC ALLERGY

*(Continued from Page 490)*

syndrome in childhood that is so intimately bound up with the status of the individual as a whole. I cannot conceive of a pediatric allergist doing a good job without first and foremost being a well trained and practicing pediatrician.

Finally, I do not believe that a single cure for allergy is at hand. I believe that allergy will afflict man as long as he retains permeable membranes, has a circulatory system, and manufactures antibodies. I have no doubt, however, that our continued earnest efforts will reduce the incidence and diminish the severity of this disease entity.

***50 East 78th Street***

# EFFECT OF VITAMIN $B_{12}$ IN ASTHMA

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MARKED improvement in a patient with asthma was noted by Wetzel et al[3] during administration of oral vitamin $B_{12}$ in doses of 10 micrograms daily. A boy with severe asthma for one year had "a remarkable attenuation of symptoms" during the first week of therapy. This case stimulated the present investigation to determine whether similar results could be obtained in other patients. Added impetus was supplied by Traina's observation that vitamin $B_{12}$ has antihistaminic action.[2] He stated that "the mechanism of action seems to be competitive antagonism [to histamine] as in the case of the common antihistaminic drugs."

Eight patients with long-standing, severe, and fairly constant asthma received various dosages of vitamin $B_{12}$* in addition to all the medication they were receiving at that time. One male, aged sixty-four, was given five subcutaneous injections of 15 micrograms each in a ten-day period. The asthma grew slightly worse during treatment. A woman, aged twenty-four, took a 5 microgram tablet twice daily for one week, followed by one tablet three times daily for one week, making a total of 175 micrograms in fourteen days. Her asthma was very severe during this time, as well as after discontinuing the drug. The third patient was a woman, aged forty, who received 20 micrograms daily for two weeks. There was no change in the severity of the asthma during or after administration of the compound. The fourth case was that of a man, aged fifty-two, who had a total of 8,100 micrograms in a ten-day period, consisting of three injections of 900 micrograms each and six oral doses of 900 micrograms each on days between injections. With each oral dose of vitamin $B_{12}$ he took 2.5 mg. of folic acid, since it has been shown that oral $B_{12}$ is much more active when given with folic acid.[1] There was no improvement in his asthma; in fact, he thought it was slightly worse. Another patient, a woman, aged fifty-six, received 10 micrograms daily for six days with no change in the asthma; after a two-week interval she was placed on exactly the same schedule as the preceding patient with identical results. The sixth case was that of a woman of sixty-two who took 10 micrograms daily for one week and stated that the mucus seemed looser, although the asthma was unchanged. After one week on a dosage of 20 micrograms daily she thought her asthma was slightly better. She then received 8,100 micrograms in ten days and felt much improved. In contrast to the other patients in this series, she had improved rapidly previously and her asthma was not usually so severe nor constant. Another patient was a man, aged thirty-eight, who took 15 micrograms daily but discontinued it after three days, as the asthma got

From the Allergy Clinic, Lenox Hill Hospital, New York, New York.
*Supplied through the courtesy of Merck & Co., Rahway, New Jersey.

worse. Later twelve tablets (60 micrograms) were administered daily for eight days with no change in his condition. He then received 9,000 micrograms in a ten-day period, consisting of two injections and eight oral doses with folic acid. There was no improvement and he felt better after discontinuing the medication. The final patient was a man of forty-seven who received 10 micrograms daily for one week, then 20 micrograms daily for another week, and after that 8,100 micrograms in ten days (three injections and six oral doses with folic acid). He noted no improvement in his condition. A few weeks later he was placed on ACTH, with almost complete disappearance of asthma within a week.

Of the eight patients to whom vitamin $B_{12}$ was administered, there was improvement in only one individual, a woman who had less constant and less severe asthma than the others and who had had spontaneous remissions in the past. Since these patients received small, moderate, and very large doses by injection and orally, alone and with folic acid, it appears that vitamin $B_{12}$ was of no value in the treatment of asthma in this limited series of eight asthmatic individuals given this type of $B_{12}$.

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## PYROMEN IN THE TREATMENT OF PERENNIAL RESPIRATORY ALLERGIES

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# GENERAL ANESTHESIA WITH CYCLOPROPANE FOR THE TREATMENT OF STATUS ASTHMATICUS

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THERE is not yet sufficient experience in the use of general anesthesia in the treatment of asthma. Doubts have been cast as to whether it is justified to make the patient run the risk, but if the cases are properly chosen, good results may be obtained.

In 1939, Meyer and Schotz[5] treated a patient in status asthmaticus successfully with cyclopropane, and for this reason this anesthetic has been used in the present series of cases.

Although cyclopropane was prepared by von Freud in 1882,[2] its anesthetic properties and low toxicity were discovered only in 1930 by Henderson and Lucas[3] in the process of purification of its isomer, propylene. Cyclopropane in anesthetic doses, according to Goodman and Gilman[1] and Hewer, does not depress the respiratory center, although the subject is deeply anesthetized; quiet breathing is maintained throughout the duration of anesthesia. In higher concentrations (36 to 39 p.c.) Seevers and Robins (quoted by Beecher) found that it paralyzes the respiratory center in dogs.

Cyclopropane has a very high anesthetic activity and can be used in mixtures with 80 to 90 per cent oxygen, thus preventing complications due to anoxia. To avoid massive atelectasis which may be fatal, an inert gas such as helium should, however, be added to the mixture.

In the treatment of status asthmaticus cyclopropane has the following advantages: (1) it does not cause an initial increase in respiratory frequency and respiratory minute volume; (2) it increases vital capacity when this is diminished; (3) it has no irritating effect on the respiratory tract; and (4) it does not depress the respiratory center.

It has little effect on the circulation. The blood pressure is not modified, although there is some peripheral vasodilatation. The heart rate does not change, or is moderately slowed. Several types of arrhythmia may occur. Ventricular extrasystoles and ventricular tachycardia are the most frequent disturbances, according to Meek's experimental observations.[4] Heart block is also seen. Epinephrine and sympathicomimetic drugs given during deep anesthesia sensitize the automaticity of the heart, and plurifocal ventricular tachycardia can be provoked experimentally. These disturbances are only functional and transitory and are seldom serious. Waters[6] found only two fatal cases of ventricular fibrillation in 7200 anesthesias. Bonham (1941) reported three cases of asthma due to cyclopropane.

The consensus of opinion (Beecher, Hewer, Dogliotti, Martinez, Good-

Approved for publication April 5, 1951.

man and Gilman, and others) is, however, that cyclopropane expertly handled does not involve circulatory risk of any importance and can therefore be used in patients with serious circulatory disturbances.

Cyclopropane is quickly absorbed and eliminated by the lungs; it does not damage the liver, provokes no toxic metabolic effects, and does not increase salivary secretion. Postanesthetic recovery is rapid and uneventful; nausea, vomiting and respiratory complications occur less frequently than with other anesthetics.

## METHOD OF ANESTHESIA

Anesthesia in status asthmaticus should be performed by a qualified anesthetist in a hospital. No preanesthetic sedative treatment has been given in this series, because most of these drugs usually employed depress the respiratory center.

With the collaboration of our anesthetist, Dr. F. Taleb, the following procedure was adopted: the period of induction was prolonged from the usual two minutes to four or five minutes in order to avoid excitation. The first stage, which lasts six to seven minutes in surgical anesthesia, was lengthened to ten or fifteen minutes so that the anesthetic could produce its maximum effect on the bronchial muscles. The second stage was also lengthened from the usual three minutes to four or five minutes for the same reason. In the third stage the patient was gradually sent into deep anesthesia and kept thus for twelve to fifteen minutes. Then the subject was wakened as quickly as possible in order to avoid bronchial stenosis, which may occur when the return to consciousness takes place slowly.

The procedure is repeated twice, in order to reinforce the effect of the first period of narcosis, except that the last time the patient is allowed to recover as usual. The whole process lasts from forty to fifty minutes. Antispasmodics, including epinephrine, have been used in the postanesthetic period, and no disturbances in the heart rhythm have been observed.

## CASE HISTORIES

*Case 1.*—A woman, single, twenty-six years old, in September, 1948, suffered from continuous respiratory dyspnea, which did not respond to the usual symptomatic treatment and gradually became worse. A month later there was permanent bronchial stenosis, which did not respond to antispasmodic drugs. There was marked cyanosis, tachycardia, blood pressure of 105/70, normal heart sounds, and wheezing throughout both lungs. The patient was in a state of anxiety, and her general condition had deteriorated. Anesthesia with cyclopropane, as outlined above, was performed. As soon as the patient entered into the third stage, wheezing disappeared almost completely. After anesthesia 2 mg of epinephrine in oil was given. Recovery was uneventful, and twenty-four hours later the patient was up and well. Specific antiallergic treatment was continued. In the subsequent two years an occasional access of asthma has occurred.

*Case 2.*—A man, married, forty-five years old, a physician, in April, 1947, was in continuous status asthmaticus for more than a week, the severity of the condition

increasing progressively. Symptomatic treatment gave little or no relief. General anesthesia was performed, and epinephrine in oil injected in the postanesthetic period. Between the third and fourth day recovery was complete. Asthma has not recurred.

*Case 3.*—A man, married, fifty-two years old, was seen in January, 1947, suffering from respiratory dyspnea so severe that speech was difficult and complete rest imperative. The subject was obese; there were wheezings and other bronchial râles in both lungs. Heart sounds were normal; blood pressure was 185/95. Symptomatic remedies had little or no effect. Anesthesia with ether by rectal infusion was performed twice without obtaining any relief. Cyclopropane anesthesia was performed thirty-four days after the patient had been seen for the first time and had been continuously in status asthmaticus. Antispasmodics were administered during the postanesthetic period. Recovery was complete and the patient dismissed eight days later.

*Case 4.*—A woman, married, thirty years old,, was first seen in 1946, but examination of her allergic condition was not then completed. A year later she was again seen in status asthmaticus, which did not respond to antispasmodic treatment. The general condition was deteriorating, and the patient was suffering from considerable nervous irritability. On the thirty-sixth day of continuous asthma cyclopropane anesthesia was performed. Pulmonary symptoms disappeared between the first and second period of narcosis. Antispasmodic drugs were given after anesthesia. This patient did not recover as rapidly as the others.

*Case 5.*—A woman, married, fifty years old, was seen on the fortieth day of status asthmaticus. She had intense dyspnea and asthenia and a considerably deteriorated general condition. The usual bronchial wheezing was observed, and a slight arrhythmia. Epinephrine was given in intravenous infusion (1 mg epinephrine and 20 mg aminophylline in 1000 cc isotonic glucose solution, 30 drops per minute) without any relief. Ether by rectum in anesthetic dose, given twice with a twenty-four-hour interval, caused little improvement. General anesthesia with cyclopropane followed by antispasmodic treatment gave considerable relief. Recovery was complete in ten days. Five months later she again suffered an asthmatic crisis, but much less severe than the previous one.

*Case 6* (Courtesy of Dr. Taleb).—A man, married, forty-six-years old, was seen in November, 1948, after fifteen days in status asthmaticus. Because he did not respond to antispasmodic treatment, general anesthesia with cyclopropane was performed; this was followed by marked improvement but not complete recovery. A second period of narcosis was administered forty-eight hours later but gave no results. The patient died in January, 1949, from cardiac insufficiency.

## COMMENTARY

General anesthesia with cyclopropane, which we consider the best anesthesia for our purpose, is a useful therapeutic measure in some cases of status asthmaticus. It is, however, only symptomatic treatment and should not be undertaken unless the patient fails to respond to the usual antispasmodic treatment. Most patients can be submitted to anesthesia although there is bronchial obstruction, in which cases bronchial aspiration should also be performed. Patients in cardiac decompensation should not be submitted to this type of treatment.

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# MINOR SYMPTOMS AND SIGNS IN FOOD ALLERGY

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IN some patients food sensitivity is so definite that it is not even questioned by the patient. More frequently, however, it may be very difficult to determine, first, whether allergy to ingestants (foods, drugs, or beverages) is an important factor in the symptoms, and second, if so, what ingestants are involved in the production of the symptoms.

Minor symptoms of food allergy may be the patient's only complaint in which incidents that are important for diagnosis and treatment are evident. Just as often, though, any one or any combination of symptoms listed below may accompany a major allergic condition and not become apparent until after proper allergic management has afforded partial or complete relief for the primary complaint. If the minor symptoms are ignored, the patient may call attention to them. If, on the other hand, they are observed by the physician, the patient may explain that he has suffered for years from this discomfort and, after much treatment without relief, had given up and that there was no use to mention the vague, but nevertheless, annoying and persistent symptoms.

That minor symptoms are important in indicating allergy to certain foods in the clinical food tests, has been brought out by Vaughan and Black[2] and Rinkel.[1]

These minor symptoms and signs are especially important in patients known to be allergic or in patients who have a strong family history of allergy, but also at times in patients when other etiological factors cannot be found for them.

As a rule these symptoms are explained by the patient in numerous ways. He may say that he is "acid," or that certain foods contain too much roughage, and he will not even suspect that allergy has anything to do with his symptom. These symptoms may be so relatively small compared to his major allergy that he does not notice that he has them. He cannot help us use these minor symptoms to determine his ingestant allergens until we teach him to watch for the symptoms and to know that food allergy may produce them.

By recognizing and treating minor symptoms it may be possible to prevent the development of major allergic disease in the future. In our experience the minor symptoms have been most evident in those who have been under treatment for chronic asthma or some other major allergic condition and have obtained relief from major allergy but who still show a persistence of minor symptoms as evidence of active allergy or the allergic state. It is here that these symptoms should help us most by mak-

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Presented at the Sixth Annual Congress of The American College of Allergists, January 15-18, 1950, St. Louis, Missouri.

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ing us suspect that allergy to foods is contributing to the patient's symptoms and discomforts and may even help us to suspect which foods are the offending allergens. It is sometimes possible to be lulled into a sense of false security by the definite improvement of the major or presenting symptoms, and to have ignored or overlooked the less obvious minor allergic symptoms that should have been very definite indications for further and broader study, including investigation of food sensitivity.

After the patient has made definite improvement from the major allergic symptoms, he may become dissatisfied with the investigation and treatment, which does not take into consideration the mild but annoying discomforts, of which he has so frequently complained, and which have not been relieved despite numerous examinations and considerable treatment.

The following is a list of symptoms which can be, and often are, due to food allergy. They may be the chief symptoms from which the patient seeks relief, but just as often are milder symptoms of irritation secondary to the major allergic condition.

*Skin.*—

1. Pruritus on any part of the body, including pruritus ani or vulvae.

2. Recurrent attacks of mild urticaria, or diffuse itching without observable skin lesions.

3. Eczema involving the scalp, hair margins, or forehead and eyebrows, which may spread over the face or, less frequently, over the chest.

4. Eczema in or behind the ear.

5. Flexural eczema of a mild nature, with exacerbations of itching and erythema.

6. Eruption on the face, with scattered, discrete, macular lesions, which itch and excoriate so easily that they may be described as "blisters" by the patient. After scratching there remains a flat, superficial excoriation, usually not infected.

*Respiratory System.*—

1. Chronic or recurring so-called "colds."

2. Chronic nasal obstruction, with or without watery drainage.

3. Mild itching of the eyes and nose, especially in children, often denied, but the patient is observed to rub his eyes and/or nose from time to time while being interviewed.

4. Recurrent attacks of sneezing, usually with some watery discharge and without itching, which the patient attributes to change of temperature.

5. Paroxysmal attacks of croup, or croupy cough, more frequent in children, but sometimes occurring in adults.

6. Recurrent attacks of coughing, without any evidence of infection and with or without mild wheezing.

7. Continued redness and granulation of the palpebral conjunctivae that show little change since the first examination.

8. Swollen, watery, pale inferior turbinates, with "pigskinning," at times without nasal symptoms, except "stuffiness," i.e., partial occlusion.

9. Canker sores in the mouth or on the lips, or "bumps" on the tongue.

10. Residual wheezing brought out by deep breathing and coughing, or by forced expiration.

*Central Nervous System.—*

1. Recurrent headaches, without definite pattern, but more likely to occur during the night or early morning hours, usually frontal or general.
2. Fatigue beyond normal, without other demonstrable cause.
3. Recurring mental and emotional upsets or personality changes, which are foreign to the patient and not present under ordinary circumstances.
4. Attacks of undue drowsiness which are foreign to the patient and not present under ordinary circumstances, likely to occur in the mid or late afternoon or after dinner in the evening, sometimes preceding an attack of migraine.

*Gastrointestinal.—*

1. Belching, bloating, colic (very frequent in children), chronic fullness, flatulence, attacks of mild nausea, recurrent attacks of mild diarrhea, regurgitation or retasting of food for some time after eating it, or heartburn occurring chronically in adults and frequently associated with a major allergic disturbance.

*Musculo-Skeletal System.—*

1. Recurrent attacks of soreness, pain and/or swelling about the joints, tendons, muscles, without fever. The attacks may recur in the same areas, but may move from place to place over the body.

*Genitourinary System.—*

1. Attacks of frequency of urination, with or without pain, and without apparent cause.

Once it has been determined that the patient exhibits one or more of the above symptoms and signs, this can be used for the retaking of a very detailed food allergy history. It is not unusual for a patient to complain of one or more or a combination of minor symptoms and signs. For example, a patient may from time to time have heartburn, regurgitation, or retasting of food, mild sneezing and watery drainage from the nose. In taking his history, then, one may ask him specifically whether he knows or suspects that wheat or wheat products, cabbage, pork, milk, or any other ingestant is a cause of one or more of the above symptoms.

We have noted so often that when we ask an allergic patient whether any certain food or foods cause him to have any unusual symptoms, he will automatically answer, "No." Frequently, when we ask him about individual food groups, such as cereals, meats, seafoods, fruits, vegetables, nuts, et cetera, he will still not be able to recall that any food seems to cause him allergic symptoms. However, if we take the time to mention individual ingestants, and at the same time remind him of the symptoms that might be caused by allergy to any one or more of these, he may then recall that a certain food might be responsible for one or more of the symptoms of which he complains.

The use of a detailed questionnaire, as suggested by Vaughan several years ago, is of very definite value. It is not only time saving but it prevents the possibility of omitting some important questions. It may be even more valuable when used at different intervals by the same patient when he returns for re-examination. By this time he has gained enough

knowledge about the symptoms and the possible relationship to food allergy that he has a better idea of what is desired by the physician.

Any food thus suspected can be subjected to clinical food tests. If the food is responsible, the same symptoms can be produced at will by taking the same food under the same conditions.

## CASE REPORTS

*Case 1.*—Mrs. G. E. B. suffered with allergic coryza and bronchial asthma for one year and was partially relieved by hyposensitization, precautions against dust, and other measures. However, she had a recurrence of symptoms from time to time. In the original history she denied food sensitivity. After going into the history more in detail, as suggested above, it was found that ingestion of bananas, cabbage, oranges, and turnips resulted in what she described as "indigestion," being largely heartburn and retasting of food for some time after ingestion. She was then given several bananas daily, and it was finally determined that if she ate as many as three bananas in one day, she could precipitate an attack of allergic coryza.

*Case 2.*—Mrs. C. N., aged forty, complained chiefly of bronchial asthma and allergic coryza. She had suspected that milk and eggs produced symptoms of coughing and wheezing. Upon questioning, she had noted also that chocolate caused small red papules on the skin, which she termed "acid bumps." Turnips or turnip greens resulted in her having two to four loose bowel movements within six to eighteen hours after ingestion. After further observation it was determined that chocolate and turnips would also cause symptoms of bronchial asthma. She also noted that raw onion and cucumber would cause headache. This patient illustrates the variety of symptoms that may occur in one person as the result of various food sensitivities. She illustrates also the fact that foods that are known to cause minor symptoms may also cause bronchial asthma.

*Case 3.*—Mr. H. S. M., Jr., aged forty-six, suffered with bronchial asthma, chiefly from known or suspected inhalants. When questioned about ingestants, he reported that he didn't think foods caused wheezing or other symptoms. Upon further questioning and later by clinical trial, it was found that he had indigestion from coffee. Honey had a laxative effect upon him. The ingestion of peanuts and watermelon caused headache. Oranges caused "acid eructations." This case clearly illustrates the necessity for taking a detailed food history, not only in relation to the individual foods, but to the major and minor symptoms as well.

*Case 4.*—Mrs. P. R. S., aged thirty, had suffered from bronchial asthma for ten years and knew that dust would precipitate an attack. She had noticed that after eating pork the roof of her mouth would itch, but did not suspect that it caused asthma. She had suspected that onions and chocolate might cause asthma, but was not sure. On clinical food tests, the ingestion of pork definitely caused wheezing and dyspnea. This patient illustrates the fact that a food that is known to cause a minor allergic symptom may also be a factor in the production of a major allergic condition, such as asthma.

## SUMMARY

Definite food allergy symptoms are not questioned by the patient, but frequently it is difficult to determine whether food allergy is a factor in the production of symptoms and, if so, which foods are acting as aller-

gens. Eliciting minor symptoms of food allergy by careful history may help answer both of these questions.

Minor symptoms of food allergy may occur alone, in which case the importance of proper diagnosis and treatment is evident. Frequently, minor symptoms may accompany a major allergic disturbance and not become apparent to the doctor and/or patient until the major symptoms are under proper control.

If a major allergic disturbance is properly controlled, eliciting minor symptoms on re-examination that may be due to food allergy may show the physician that the patient is still in an active allergic state, that treatment cannot be relaxed, and that the investigation of the presence of food allergy must be pursued further. Careful history here is important, because the symptoms may have been dismissed by the patient because of frequent negative examinations or poor results from previous treatment. By recognizing and treating minor symptoms, the occurrence of major symptoms may be prevented.

After the patient has made definite improvement, he may be dissatisfied with the treatment or investigation which does take into consideration mild symptoms which have been present for many years and yet have not been relieved by past examinations and treatment.

A list of minor symptoms which may be due to food allergy is given. History taking in relation to minor symptoms is discussed. Short, illustrative histories are given.

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*207 Doctors Building*

## ANESTHESIA IN STATUS ASTHMATICUS

*(Continued from Page 521)*

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# The Editor's Page

DURING the last two months a number of reports have appeared concerned with allergic reactions to drugs, some old, some new. The exact manifestations can be culled from the titles of the papers given in the bibliography below.

Among others, antihistamines are reported as causing angioneurotic edema,[10] local cutaneous sensitivity,[18] and toxic effects.[25] Epinephrine is described as, itself, the cause of urticaria[11], and ACTH as responsible for anaphylactic shock.[6] Aspirin ingestion can evidently cause a mild Cushing's syndrome,[3] and quinidine, an exfoliative dermatitis.[23] Additional case reports of sensitivity to codeine,[19] to mercurial diuretics,[8] to iodized oil used bronchographically,[22] continue to appear. Furacin, used topically, may result in extensive dermatitis.[20] Allergic manifestations may be due to agar.[5] Chloromycetin,[1] streptomycin,[4] and penicillin[7,12] continue to be reported as producing allergic reactions.

It is the general consensus that reactions to penicillin are increasing in number. Timely, therefore, is the study by Kitchen and his associates,[14] who report that in a recent poll of fifteen prominent investigators extensively experienced with penicillin, eleven asserted that the trend in reactions has been downward; three stated that there has been no change; and one did not answer the questionnaire. On the other hand, recent literature would lead physicians to believe that the tendency to penicillin reactions had actually increased. What are the facts? At Bellevue the reaction rates for 1947-1950 were respectively, 4.65, 3.74, 3.42 and 3.38. Although there are more papers dealing with penicillin reactions, much more penicillin is being used. In four years, the production of penicillin has increased from 41 to 177 trillion units. For these same years, reported reactions are, respectively, 136, 127, 135, and 148. It may be that since the reports on penicillin reactions are "old stuff," so many having been published and no new types of sensitivity having been discovered, the actual true figures are quite different. In any case, the incidence, if all the penicillin manufactured was used therapeutically in humans and all reports of sensitivity had been published, is lower. If the figures for the reports are correlated with the trillions of units manufactured during the four-year period, the respective reaction rates are 3.31, 1.33, 1.2, and 0.84.

In the practice of the editor and his colleagues, the incidence of reactions, chiefly urticaria and "ids," occur in approximately 7 per cent of all patients, some of whom are part of an "allergic population," others of whom are referred for penicillin reactions alone and suffer from no other form of allergy.

For these patients, there is good news. Every internist who has treated a patient extremely sensitive to penicillin wonders what he will do the next time the patient becomes infected with bacteria for which penicillin is the drug of choice. A new biosynthetic analogue, Penicillin O,[24] and two new salts of penicillin are reported as stable and therapeutically effective. One[17] has a low reaction rate, and the other,[13] is antiallergic in its effects.

Although many American allergists have reported penicillin to be without benefit in the majority of infectious asthmatic patients, communications concerned with its beneficial effects continue to appear. According to Lillienfeld-Toal,[16] cure or marked improvement was noted in twenty-three of thirty patients given penicillin or streptomycin. Especially helped were those whose sputum contained streptococci or hemolytic staphylococci (benefited by penicillin), or *B. coli* (benefited by streptomycin).

In the treatment of bronchial asthma, also, a venturesome American investigator might wish to corroborate the work of Gelato,[9] who administered curare intravenously in doses of 1.5-3 mg to six patients with bronchial asthma. The dyspnea was suppressed for twenty minutes to fourteen hours, the effects being reported as being quicker and longer-lasting than those of epinephrine. There were no side reactions.

The antihistaminic drugs continue to be responsible for a good deal of the literature. Clinical reports on new antihistamines, and on those long since evaluated, are being published in large numbers. Of special interest is a communication by Monash and Guiducci,[21] showing that tolerance results if any one antihistaminic agent is taken for seven days. The effect on a histamine phosphate wheal produced electrophoretically shows the maximum effect with each new antihistaminic agent, such effects lessening day by day. Rotation of antihistaminic agents each week gives the maximum results. The earlier drugs used regain their effectiveness in about four months.

Intravenous Pyribenzamine has been shown to inhibit electrophoretically produced histamine wheals,[15] the drug achieving its maximum results in two hours and lasting about five hours. The delayed action tablets are effective in about five hours and last an equal period of time. Doubling the dose from 50 mg to 100 mg doubled the antiwhealing effects.

The following notes are published without comment. In an interview with a reporter for *Drug Trade News*, John W. Clissold,[2] Director of Sales for the Anahist Company, stated that kits of display material for the fast relief of head colds, hay fever, and other allergies have been sent to virtually all retail druggists and chain stores throughout the United States. "We are convinced," said Mr. Clissold, "that there exists at the present time an almost completely undeveloped market for spring allergy remedies. Many, many people who claim that they have spring colds really have an allergy, and frequently these so-called colds are not difficult to throw off, but because they are allergies, do not respond to the usual cold medica-

tion." The promotional material points out that 6,000,000 persons will have nasal allergy this spring. According to Mr. Clissold 95 per cent of all doctors prescribe antihistaminic agents for hay fever and 73 per cent prescribe them for colds.

Character Products Company in New York has invited druggists to turn in their old stock of Millan tablets. The tablets have been repackaged and relabeled. The company has announced that it has begun consumer advertising in the New York City area with a series of television talks scheduled for twenty-six weeks. These, given by Dr. Frederic Damrau, will be entitled "Healthy Humans." The station is WOR; the time, 10:30 a.m., every Sunday. The tablets? They are used for the symptomatic relief of hay fever and bronchial asthma.

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# Progress in Allergy

## CONNECTIVE TISSUE REACTIONS

### A Critical Review

### I. Effects of ACTH and Cortisone on Allergic Reactions and the Collagen Diseases

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THE background of the development and clinical application of ACTH and cortisone is a fascinating one, but since it has been amply reviewed,[47,91,99] the present review will emphasize chiefly the experimental and clinical data related to the effects of these drugs on allergy and anaphylaxis as well as to the clinical application in the collagen diseases (rheumatic fever, disseminated lupus erythematosus, dermatomyositis, scleroderma, and acute glomerulonephritis). The physiologic basis for the clinical improvement obtained in the therapy of the collagen diseases may or may not be found in the observations recorded to date. It seems obvious to the reviewer that our knowledge to date of the physiologic effects of these hormones is still fragmentary, in spite of the large volume of published data and the increasing emphasis on research in this field. It is, at the present time, a patch quilt rather than a tapestry, and this state of incompleteness is of necessity reflected in this review. Some of the data has been included, therefore, even though its relationship to other observations is not clear and may indeed be contradictory, with the expectation that studies in the future will clarify its importance.

The striking results obtained in the treatment of such obviously allergic conditions as asthma with ACTH and cortisone have led to a great deal of research on the basic effects of these hormones on the hypersensitivity phenomenon. One of the most striking of these is the Shwartzman phenomenon.[88] The relationship of this to the collagen diseases has been discussed in a previous review.[65] Briefly stated, Shwartzman discovered in 1928 that when an intradermal injection of culture filtrate was followed after some hours by an intravenous injection of the same material, a reaction showing marked hemorrhagic necrosis appeared in the skin at the site of the original injection. The phenomenon can be produced with culture filtrates from a wide variety of unrelated bacteria, and the preparation and provocation may indeed be accomplished by filtrates of different organisms as well as by combinations of various antigens and antibodies, tissue extracts, et cetera. It has been demonstrated[92] that the polymorphonuclear leukocytes play an important role in the pathogenesis of the Shwartzman phenomenon, and it was suggested that their presence in the prepared skin might account at least in part for the increased aerobic glycolysis exhibited by the tissue at the site of the preparation. The Shwartzman phenomenon can be inhibited by pretreatment of the rabbits with nitrogen mustard, x-rays or benzene,[4] agents which are known to produce leukopenia. The administration of nitrogen mustard is followed by lymphopenia developing within a few hours and becoming most marked at eighteen to twenty-four hours. Granulopenia occurs later, becoming maximal between seventy-two and ninety-six hours. Interestingly enough, the Shwartzman phenomenon is inhibited in rabbits treated with nitrogen mustard

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during the period of maximum granulopenia. When the bone marrow is protected from the effects of nitrogen mustard by a special technique[52] so that granulopenia does not develop, the animals show the typical Shwartzman reactions. Similar inhibition of the Shwartzman phenomenon has been demonstrated with benzene.[63] It seems obvious that there are at least two components to the production of the Shwartzman phenomenon, the first being cellular and the second related to the tissue of the animal. It seemed natural, therefore, that the new hormones noted for their effect on the host tissue should be studied with relationship to the Shwartzman phenomenon. It was shown[89] that small doses of ACTH did not prevent the tissue reaction, but that it was capable of preventing the hemorrhagic necrosis at the site of the preparatory injection after the provocative injection was given. The phenomenon was prevented in eight out of ten rabbits when 12.5 mg of ACTH was injected intramuscularly two hours before the provocative injection. Similar amounts of ACTH had no inhibitory effect when given on the day preceding the preparatory injection of meningococcus toxin. When the dose was increased, ACTH or cortisone was each found to produce hemorrhage and necrosis at the point of preparation without the provocative injection being given.[97]

As reported by these authors, in untreated rabbits hemorrhage does not occur in skin sites prepared with meningococcus toxin until after the injection of provocative material eighteen or more hours later. In control animals the skin areas injected with toxin became reddened and slightly edematous after four hours, and after twenty-four hours showed pink, slightly elevated, indurated swellings with no hemorrhages or dilated vessels. In contrast, rabbits receiving ACTH showed the following changes in the skin areas prepared with toxin. When ACTH was given before or at the time of the intradermal injection, edema and erythema were slight or did not occur. When ACTH was started after edema had already appeared, the edema subsided within a few hours. In all of the treated rabbits petechiae appeared in the injected areas, in some cases becoming gross hemorrhagic lesions. These lesions did not have the typical appearance of the Shwartzman reaction. Moreover, the lesions developed gradually in contrast to the rapid development of hemorrhage in the Shwartzman reaction. The authors suggested that it is possible that the skin reactions in ACTH or cortisone treated rabbits are based on a mechanism different from that of the Shwartzman phenomenon. It is also of interest to note that bilateral cortical necrosis of the kidneys has been produced in cortisone treated rabbits by a single intravenous injection of meningococcus toxin.[96] It would appear that the effects of cortisone and ACTH are not always beneficial but that in any case profound tissue changes are produced.

Rich and co-workers[5,6] have shown that when hypersensitivity was produced in rabbits with horse serum in a manner which had previously been shown to produce acute arteritis and cardiac inflammatory lesions, the course could be markedly altered by ACTH. In sensitized animals treated with ACTH only 25 per cent of the animals showed such lesions as compared to 90 per cent of the animals in the control group. Under these conditions it seems that ACTH exerts an inhibitory effect on the development of cardiovascular lesions of hypersensitivity. In a later study these observations were extended, so that the lesions of hypersensitivity were produced in fifty-one out of fifty-nine rabbits not receiving ACTH and in only fourteen out of fifty-nine of the ACTH treated rabbits. In this later study it was shown that the adrenals of the treated animals showed marked loss of cortical lipoid material. This loss of cortical lipoid following ACTH administration has also been found by Sayers[79] and has been denied by Selye.[83]

Studies of the intradermal skin reactions to tuberculin in humans have been carried out by Long.[58] In thirty-four patients ACTH and cortisone produced a decrease in induration and necrosis. The most readily altered phase of the tuberculin-type re-

action is necrosis, next the prevention of induration, and last the abolishment of erythema with sufficient dosage. Within thirty-six hours after cessation of treatment many of the patients showed a flaring up of the reactions, often going on to necrosis. This occurred as long as one week after the initial injection. Re-treatment again caused the lesions to subside. Since tuberculin has a specific cytotoxic effect on the leukocytes[12,25,26,31,76] and since ACTH and cortisone also have marked effects, the results with tuberculin-type reactions may be significant. All these observations indicate that tissues hold tuberculin during the period of treatment with ACTH and cortisone and that this apparently is released later.

One unusual effect of cortisone and ACTH was produced by Rich,[75] who showed that while they both inhibited the development of cardiovascular lesions and the development of proliferative glomerular lesions, cortisone produced severe glomerular damage with hemorrhage similar to the acute phase of hemorrhagic glomerulonephritis. The cortisone treated animals also showed lipemia, increased glycogen in the liver, and extramedullary hemopoiesis in the spleen.

Germuth and Ottinger[34] have shown that cortisone and, to a lesser degree, ACTH suppress the development of the allergic state ordinarily produced in the rabbit by repeated intracutaneous injections of crystalline egg albumin. Six out of eight control animals showed large hemorrhagic and necrotic skin reactions following a preliminary period of sensitization. Only three out of seven of the ACTH treated animals and none out of eight rabbits receiving cortisone showed lesions of similar severity. In all three groups there was a close correlation between the level of antibody nitrogen and the severity of the skin reaction. These authors concluded that the inhibitory effect of cortisone and ACTH on the development of the Arthus phenomenon results from the ability of these hormones to suppress antibody formation. They noted that treatment with cortisone and ACTH did not alter the animal's ability to produce the Arthus reaction when antibody was injected intramuscularly. During the passive Arthus reaction all of the animals reacted in the same way and to the same degree, regardless of treatment. These data must be interpreted as showing that ACTH and cortisone inhibit the production of antibodies, and thereby prevent a reaction in an animal whose capacity to react to antigen-antibody combination in the tissues is not altered. Some other work supports this conclusion. For example, Eisen[20] has shown that there is no increase in circulating antibody or gamma globulin as a result of adrenal cortical activity, and Mason[59] and Forsham[29] report the same findings after ACTH administration. In humans the administration of corticotropin does not produce a rise in antibody titer previously produced with staphylococcus toxoid.[48] However, in animals adrenal cortical steroids or adrenotrophin has been shown to produce an anamnestic reaction,[18,39] and also to produce a marked rise in antibody titer in an immune or hyper-immune animal.[11,19,30] This is not true in adrenalectomized cats maintained with DOCA.[95] Increase in free antibody has been recorded *in vitro*.[77]

ACTH or cortisone given before the injection of a shocking dose of tetanus antitoxin horse serum in sensitized guinea pigs failed to alter the course of anaphylactic shock.[32] Fischel reports that the administration of cortisone to sensitized rabbits was ineffective in altering the active or passive Arthus phenomenon.[28] Stollerman and co-workers[94] studied the effect of cortisone on passively induced skin hypersensitivity in humans and concluded that cortisone does not interfere with the passive transfer of skin-sensitizing antibody and does not inhibit the wheal and erythema type of hypersensitivity resulting from antigen and antibody union in the skin of human beings. In one of their cases there was inhibition of the tuberculin test.

Further information on the effect of ACTH and cortisone on antibody formation is given by some observations of Dameshek,[16] reporting on five cases of acquired hemolytic anemia treated with adrenocorticotropic hormone (ACTH). Three cases

were of the "symptomatic" variety, being associated with lymphosarcoma or lymphocytic leukemia, and the other two were "idiopathic." All cases had circulating hemagglutinins and a positive Coombs test. Each patient received intensive ACTH therapy followed by maintenance therapy in all cases but one. Four of the five patients showed almost complete remissions of the hemolytic process. Simultaneously, there was disappearance of "warm" hemagglutinin and marked diminution of cold hemagglutinin. The Coombs test remained positive in all cases. Relapses in the hemolytic process occurred shortly after cessation of therapy in two cases (Cases 1 and 2), and resumption of therapy resulted in a second remission. It is suggested that the favorable effect exhibited by ACTH on this type of hemolysis is dependent on interference with agglutinin production presumably by regression of lymphoid tissue, in which agglutinin may be produced. The stimulatory effect of ACTH upon bone-marrow activity may result in a further beneficial effect. The disappearance or diminution of hemagglutinin activity suggests that ACTH exerts its favorable influence by altering the pathologic antigen-antibody system.

With regard to tuberculin sensitivity Harris and Harris[42] found that rabbits and guinea pigs sensitized to tubercle bacilli showed suppression of cutaneous sensitivity to OT during treatment with cortisone. In guinea pigs only there was inhibition of systemic shock. There was no effect on the local Arthus reaction in the rabbit. These contrasting results again point to some difference in the mechanism of the antigen-antibody reactions *in vivo,* such as the Arthus phenomenon and anaphylaxis on the one hand and the bacterial type of hypersensitivity, such as the tuberculin reaction, on the other. It is interesting to note that four days after treatment was stopped the skin tests again became positive. Stoerk also reports inhibition of the tuberculin reaction by cortisone in hyperimmune guinea pigs,[93] while anaphylaxis is inhibited by cortisone in the rat[82] but not by ACTH in the guinea pig.[56]

Germuth[33] found that the microscopic appearance of the Arthus reactions in the treated rabbits (ACTH and cortisone) differs from that of the controls. The untreated animals showed extensive edema, hemorrhage, and acute inflammation, while the treated rabbits showed only slight edema and leukocytic infiltration. In the skin of five out of six control animals there were extensive vascular changes, consisting of focal fibrinoid degeneration, inflammation, and thrombosis of the smaller arteries, similar in all respects to those of periarteritis nodosa. In the hearts of four out of six control animals there were areas of interstitial myocarditis. These lesions were not observed in rabbits receiving ACTH or cortisone. Both ACTH and cortisone produced a marked alteration in the lymphoid tissue. In the ACTH treated rabbits there was atrophy of the thymus, occasional atrophy of the spleen, and a reduction in lymphocytes in the blood. With cortisone these changes were even more extensive. In the animals treated with cortisone the adrenals were small, while in those treated with ACTH the adrenals were large but poor in lipoid. These experiments were done with crystalline egg albumin.

Carey et al studied the effect of ACTH and cortisone on drug hypersensitivity reactions.[9] They reported a case of hypersensitivity to iodine due to the administration of hydriodic acid syrup. The patient had a very severe reaction with an exfoliative dermatitis. After he was given ACTH, the high fever, angioneurotic edema, ulceration of the mucous membrane of the mouth, exfoliative dermatitis, and disorientation rapidly improved. He had a moderately severe relapse but showed a second prompt recovery when the drug was readministered. They report the same beneficial effects in five patients who reacted to penicillin. The five patients had reactions of the serum sickness type. In one patient to whom large doses of cortisone were given, the definite beneficial effect was delayed and not so complete as with ACTH therapy. Recurrence of the urticaria five to fourteen days after stopping treatment in four of the cases indicated that the improvement was most likely due to the drug and that the sensitivity itself had not been eliminated.

The Carey group also reported a severe reaction to locally applied atropine in a patient with tuberculous uveitis. The cutaneous patch test to atropine was strongly positive. During ACTH administration there was rapid healing of the skin lesions, and the patch test produced only a moderate erythema. Another patient with sympathetic ophthalmia and an atropine sensitivity showed a similar reaction. Two cases of dermatitis herpetiformis, which were treated with sulfapyridine and developed a severe reacation with fever, dermatitis, and agranulocytosis, were treated with ACTH: in the first one there was an increase in granulocytes, but the patient died in uremia; the second case had a bullous dermatitis and leukopenia secondary to sulfadiazine and was rapidly improved. One patient with lupus erythematosus developed a hypersensitivity reaction to 3-hydroxy-2-phenyl cinchoninic acid, characterized by fever, headache, erythema of the skin, and conjunctivitis. When ACTH was given in a dosage of 200 mg there was a marked fall in temperature and rapid resolution of the reaction. Another patient with severe intrinsic asthma was sensitive to aspirin. The administration of large doses of ACTH did not prevent the development of a mild attack of asthma following the oral administration of 130 mg of aspirin. After ACTH was stopped, the aspirin was found to be less active, and the therapy may have resulted in partial desensitization.

In another case the administration of 450 mg of ACTH in a period of five days to a patient with paroxysmal cold hemoglobinuria, the titers of cold agglutinin, cold hemolysin, complement or reagin did not change significantly. Chilling the foot of the patient both before and after such therapy produced hemoglobinemia and hemoglobinuria. However, the hives and itching of the skin of the chilled foot did not appear after the ACTH injections, while at the same time the patient reacted to histamine injected intracutaneously with the formation of a typical reaction.

The mechanisms which are responsible for the beneficial effects of ACTH and cortisone on the hypersensitivity reactions are not clear. It is stated that the flare-and-wheal reaction, of which giant urticaria is an example, is the result of three stages: first, the release of the H-substance of Lewis, owing to the stimulus of a local antigen-antibody reaction or to mechanical cellular injury, and in consequence the release of histamine. The second step is the flare, probably an arteriolar dilatation, the result of an axon reflex. The third step, the central blanched wheal, results from more severe damage to capillary endothelium by the H-substance. In many cases reported by these authors[9] and others, the intracutaneous injections of histamine given to individuals being treated with ACTH never showed any evidence that the local cutaneous reaction to injected histamine had been suppressed. The reaction to curare, thought to be due to the release of naturally occurring histamine at the site of injection, is not blocked by ACTH either. Similarly, in the patient with paroxysmal cold hemoglobinuria the development of the urticaria was blocked, but the hemolysis of red blood cells was not altered.

It can be seen that the mechanism by which ACTH and cortisone benefit the hypersensitivity reactions is not well understood. Neither do we understand the reasons for the beneficial effects reported in the collagen diseases. Observations that patients under treatment with cortisone or ACTH show delayed wound healing,[15] as well as similar observations in animals,[73] and also the immunological studies reviewed above lead to the obvious conclusion that ACTH, cortisone, and the hyperadrenal state in general only inhibit the reactivity or the response to trauma on the part of the connective tissue,[71] and that since the precipitating traumatic factors are not affected relapses should not be unexpected when treatment is discontinued.

There has recently been a great deal of interest in hyaluronidase and hyaluronic acid and in the reactions of the ground substance in inflammation in general.[66] In this case it should be noted that ACTH administration results in a marked decrease in the level of nonspecific serum hyaluronidase inhibitor in patients with

rheumatic fever.[17] This decrease parallels the drop in sedimentation rate and the clinical improvement. The authors suggest that this may be a reflection of the effect of adrenal hormones on changing the state of connective tissue so that it no longer reacts to the precipitating stimuli in the diseases of connective tissue. A fall in serum hyaluronidase inhibitor is also reported by K. Shuman[87] and C. R. Shuman.[86] Opsahl[68] has noted that the intracutaneous spread of India ink was increased by adrenalectomy and hyaluronidase, and the inhibiting effect on hyaluronidase of corticosteroids has been demonstrated conclusively.[69,103] Cortisone has an anti-hyaluronidase effect[81] *in vivo* but not *in vitro*.[102]

There is a group of observations whose place it is difficult to determine in the over-all scheme of the method by which ACTH and cortisone affect hypersensitivity reactions. The profound cellular effects have been described.[99] The report of Spain and Thalhimer[90] points out that in Swiss albino mice injected with cortisone, eight hours after the injection the spleens contained a larger number of eosinophilic leukocytes than normal. The authors suggest that the spleen may be the area where eosinophilic leukocytes are withdrawn from the circulation following adrenal cortical stimulation.

ACTH and cortisone also have marked effects on plasma proteins. Vaughan[100] reports that both ACTH and cortisone therapy depress the gamma globulin and fibrinogen levels in the blood of patients with active rheumatoid arthritis and scleroderma. Changes in these blood proteins are probably responsible for the changes in the sedimentation rate.

Reiner[74] showed that in twenty cases of disseminated lupus there was a lowering of the albumin level with a considerable increase in the a-2 as well as gamma globulin concentration. Five patients were studied before and after treatment with cortisone and ACTH. After clinical improvement it was found that the albumin and gamma globulin components tended to return to normal, while the a-2 globulin fraction remained unchanged. In healthy human subjects the serum protein components are not changed by the administration of these hormones.[78]

Marked effects on lipids have also been noted. Levin and Farber[57] point out that many pituitary preparations produce an increase in liver fat in mice. This response is completely abolished by adrenalectomy. Neither cortisone nor any other adrenocortical steroid tested to date is able, of itself, to cause a substantial increase in liver fat in the intact or adrenalectomized mice. In the latter, however, it prevents the usual loss of liver fat after adrenalectomy. When pretreated with cortisone, the ability of adrenalectomized mice to respond to pituitary hormone by mobilization of fat to the liver is equal to or greater than that of intact mice. They concluded that to mobilize fat from the body to the liver the animal requires at least two factors: (1) adequate supplies of adrenocortical hormone plus (2) a supply of an as yet unknown "triggering" pituitary factor. This factor does not act through the adrenal cortex, since it operates in the absence of the adrenal gland provided that adequate amounts of exogenous cortisone are given.

Increases in serum lipids have also been reported by Adlersberg,[1] who showed that both ACTH and cortisone produced changes, cortisone being the most striking. With cortisone there was a significant increase in total serum cholesterol and phospholipids with a decrease in neutral fat. These changes were noted in two patients even while they were on a fat-free, cholesterol-free, sodium-free diet. The fasting sera in seven of the fifteen cortisone treated patients and three of the twelve ACTH treated patients became lipemic despite the fact that the level of neutral fat had decreased. These observations are interesting in the light of the possible role of lipids in arteriosclerosis and degenerative arterial lesions, but the connection is at present not obvious.

## CLINICAL OBSERVATIONS

There have been many reports on the beneficial effect of ACTH in *disseminated lupus erythematosus.* In summary, it might be said that ACTH produces a marked improvement in the majority of cases during the acute phase. It is probable that the ultimate outcome of the disease is not permanently affected except for saving from death some of the acute cases. The course of the disease following the initial improvement is probably determined mostly by the permanent damage done to the organs by the disease.

Thorn[98] has described the beneficial effects of ACTH on six patients with disseminated lupus erythematosus. Of these six cases, two were acute; five out of the six were females. ACTH was given in doses of 40 to 100 mg per day. In one patient ACTH was administered continuously for seventy-three days, but in the others one to four courses of treatment were given, a single course usually lasting ten to thirty days. The rapid disappearance of fever within forty-eight hours and of skin lesions within five days was striking. In cases receiving several courses of treatment the fever reappeared a few days after ACTH had been discontinued, but again responded to ACTH therapy. The fever was unaffected during a second and third course of ACTH in one of the patients, and it is interesting to note that this patient failed to show significant adrenocortical stimulation as measured by the urinary excretion of 17-ketosteroids. There was marked improvement in joint symptoms where present within eight to twenty-four hours, and improvement in this respect appeared to be permanent. A marked reticulocyte response was noted,[99] and in one patient with marked bone marrow hypoplasia of the red blood cell series there was a complete hematologic remission for two months. In another patient with severe agranulocytosis there was a temporary increase in circulating granulocytes which lasted only during the period of ACTH administration. In one patient "L.E." cells were found in the bone marrow, but after ACTH therapy these cells could no longer be demonstrated. Thorn recommends the measure of 17-ketosteroid excretion to measure the degree of adrenocortical stimulation, since these patients already have an eosinopenia. Thorn's observations also indicate that the sedimentation rate is not a reliable measure of remission, although a fall in sedimentation rate, following the initial elevation after ACTH is given, usually indicates that the disease is being favorably influenced by ACTH. In one of these patients with severe renal damage there was improvement of the urine findings, and this improvement appeared to be long-lasting. The other patients showed little change in the urine. In general nitrogen retention in the blood was also reduced, except in one patient who had very severe renal damage. They report the death of one case which was not improved. Their youngest patient, eighteen years of age with a very acute type of disseminated lupus erythematosus, received 6.5 gm of ACTH and apparently has shown a complete remission of six months up to the time of reporting. Remissions have been reported also by Elkinton[21] and by Bordley.[7] Baehr and Soffer[2] have reported remissions in five cases treated with 150 to 200 mg of cortisone or 100 mg of ACTH per day, and temporary remissions have also been recorded by Plotz et al,[70] Schwartz and Sonne,[80] Grace,[36] and Ferriman.[27]

Brunsting et al[8] report their experience with the treatment of seven cases of acute disseminated lupus erythematosus with cortisone. In their first case with a dose of 100 to 150 mg three days a week, the signs and symptoms, including the polyarthritis, polyserositis, fever and tachycardia, responded permanently. The sedimentation rate, albuminuria, leukopenia, and albumin globulin ratio showed improvement and the general health was improved. There was also a reduction in the number of "L.E." cells found in the bone marrow during treatment, but these did not entirely disappear. The second case showed that large doses of cortisone were needed during the early acute phase of the disease and that the symptomatic response was maintained

for almost two months after a course of treatment lasting twenty-one days. In this case, however, the laboratory findings were not affected; and hematuria, albuminuria, and fever were the first evidences of relapse. In this case death was due to marked peripheral edema, pleural effusion, and pulmonary edema. The necropsy showed atrophy and loss of lipoid of the adrenal glands, and it was felt that the cortisone had caused a gradual retention of salt and water which combined with the severe renal damage to produce death. The autopsy also revealed the typical findings of lupus erythematosus in the heart and kidneys. Their third case first received ACTH, but this was stopped because of the sudden onset of symptoms suggesting intestinal perforation. Later cortisone was given and the symptoms brought under control, but the administration of the two hormones masked signs of complicating infection, such as peritonitis and the development of multiple peritoneal abscesses. This patient also died, death being due to chronic infection and inanition. In this patient the number of "L.E." cells in the bone marrow was not reduced. The last three cases reported show no other features of note except that in one the "L.E." cells in the bone marrow were again not reduced. One patient died and the other two appear to be going downhill. The seventh case is significant in that when the intake of salt was restricted there was absence of fluid retention during cortisone therapy. Unfavorable reactions to cortisone were common. The clinical analysis in these cases leads to the conclusion that cortisone and ACTH during the acute phase promote remissions, but that the benefits tend to be temporary. It is also to be noted that the autopsy findings on patients who died showed no change in the typical pathological lesions of disseminated lupus erythematosus.

Irons et al[51] studied eight cases of disseminated lupus, one case of periarteritis, one case of scleroderma, one case of discoid lupus erythematosus, two cases of psoriasis and arthritis, one case of exfoliative dermatitis, one case of superficial allergic dermatitis, and one case of dermatitis herpetiformis. A marked difference was noted between the effects of ACTH and cortisone. In disseminated lupus ACTH induced faster remissions, but maintenance on cortisone is suggested. Skin biopsies carried out during the period of study correlated well with the clinical evidence of improvement but did not show a complete reversion to normal.

Carey et al[10] report their experience in the treatment of twelve patients suffering from disseminated lupus erythematosus and treated with ACTH and cortisone. In general, the results were good, and complete remissions lasting up to eleven months were noted following a single course of treatment. Five patients had extensive skin lesions without any outstanding systemic lesions. Four of these were treated with ACTH and one with cortisone. Excellent results were obtained in three of these. A patient with periarteritis nodosa was treated with ACTH. Serial biopsy in this case showed progressive healing of the arterial lesions during the course of the therapy. It should be noted that it would be well to differentiate sharply, in reporting the results of therapy, between cases of discoid lupus erythematosus and cases of disseminated lupus erythematosus, as the results obtained in two groups indicate that more beneficial results are found in the discoid type, whereas in the disseminated type only temporary remissions are obtainable at best.

It should be mentioned that several observers have noted the disappearance of "L.E." cells[40,43,44] during the course of treatment with ACTH.[10,47,99]

The effects of ACTH and cortisone on *scleroderma* have not been striking. Bayles et al[3] have treated four cases of scleroderma with ACTH in doses of 5 to 10 mg every six hours. There was some improvement during treatment, particularly with reference to joint pains and joint stiffness, but none of these effects were maintained after the drug was stopped, and all patients reverted to their former state within two or three weeks. Thorn et al[99] report no relief in a patient after two weeks' treatment with ACTH in doses of 25 to 40 mg every six hours, while a second

patient, whose symptoms were principally joint pain and stiffness, received only moderate relief from cortisone in doses of 25 to 50 mg every six hours for three weeks. Hines et al[50] studied the effect of cortisone and ACTH on the peripheral circulation and blood pressure in three patients with scleroderma of the acrosclerosis type following the administration of cortisone and on one patient following the administration of ACTH. They found a gradual but slight increase in the blood flow in the arms and legs, which lasted for more than one and one-half hours after administration of 100 mg of cortisone. No marked change was noted when the dose was increased to 300 mg. There was no significant change in skin temperature or blood pressure after administration of either cortisone or ACTH. These studies indicate that the effect is probably transient and not cumulative, agreeing more or less with the clinical observations in these cases. The most enthusiastic report is that of Sharnoff,[84] who reports the case of a forty-one-year-old housewife, whose disease was marked by multiple joint pains and swelling and progressive tightness and thickening of the skin of the face, chest, and extremities. There were also cyclic episodes of deep pallor or cyanosis of the fingers when exposed to cold. The patient was given 300 mg of cortisone the first day, 200 mg the second day, and 100 mg daily thereafter. On the day following inception of treatment there was dramatic improvement. The patient was able to move about freely without pain, and three days later she walked without difficulty and was able to bend and touch her fingers to the floor. After eight days of therapy some joint pains reappeared, but in general she was much improved and was discharged to receive further cortisone therapy at home. However, two months after therapy was begun there was noted a gradually increasing blood pressure. Cortisone was discontinued and ACTH was given instead, but this was also discontinued because of further rise in blood pressure and peripheral edema. The patient died ten weeks after treatment was begun, the final episodes being indicative of uremia. At autopsy severe arterial lesions were found in the kidneys with marked increase in the intima. Some vessels were occluded by thrombi, and there were wedge-shaped areas of infarction scattered throughout the cortex. Vesicular changes were also found in the arterioles of the pancreas, where there was also marked infiltration of the adventitia by lymphocytes and eosinophiles. Although the clinical improvement in this patient was striking, the authors point out that the thrombotic infarctions of the kidneys may have been related to the administration of cortisone and that treatment with these hormones may have accelerated the development of the pre-existing vascular lesions. They also suggest that possibly the hypocoagulability of the blood which can occur with cortisone and ACTH[14] may have played a part in the formation of vascular thrombi in the kidneys.

Indirect evidence points to an endocrine factor in scleroderma.[49] For example, there are creatinuria, negative nitrogen balance, occasional low serum sodium and chloride levels, and low urinary 17-ketosteroid excretion. The preponderance of the disease in females and its close relationship to menstruation and menopause are suggestive of gonadal or adrenal hypofunction. The low FSH titers and low 17-ketosteroid excretion also suggest changes secondary to pituitary dysfunction. Administration of ACTH produced definite increases in urinary 17-ketosteroid excretion. Treatment with testosterone propionate produced marked clinical improvement as well as amelioration of the esophageal involvement as shown by roentgenograms, and the improvement was maintained four to five months after therapy was stopped.

The results obtained in *dermatomyositis* have also been variable and temporary. In only one case[67] there was a dramatic recovery following a total dosage of 4 gm of ACTH given during a period of fifty-three days. Ragan[72] reports only temporary benefit in two patients treated with ACTH in doses of 100 mg per day. A preliminary report of Elkinton[21] is not much different. Thorn[99] reports good clinical improvement in two patients, one a nine-year-old girl and one a six-year-old girl, and only little improvement in an adult female. The nine-year-old girl had a two

months' history of progressive muscular weakness, swelling over the eyes and cheeks, and a rash over the cheeks, elbows, and knees. After five days of treatment with ACTH there was some improvement in the skin rash and a slight increase in muscular strength. A biopsy taken on the ninth day after treatment showed reduction of lymphocytic and mononuclear infiltration and reduction in the amount of interstitial edema. After sixteen days of treatment the skin rash had almost completely disappeared and there was some increased muscle strength. Following this improvement with ACTH she was given testosterone propionate with further improvement. The six-year-old girl had acute joint symptoms for two months, followed one month later by progressive weakness of the neck, back, and respiratory muscles, so that it was found necessary to place her in a respirator. Ten days after treatment she could be out of the respirator for eight-hour periods, but a biopsy taken on the fourteenth day of treatment did not show the same marked improvement as was shown by the first case. After three weeks of treatment with ACTH the patient no longer required the respirator, and there was improvement in the strength of her neck and back muscles. She was also given testosterone propionate, and six months later she was able to carry on limited activity. The adult female was given 100 mg daily of cortisone for three weeks with little improvement, although ACTH apparently produced slight improvement. These authors point out that ACTH is capable of altering the acute process in the muscles but that no lasting remission appears likely unless the cases are treated early and vigorously. It certainly is interesting to note that the two cases markedly benefited by ACTH were in very young girls. The authors also suggest that testosterone propionate be used after the initial improvement with ACTH is obtained.

In *periarteritis nodosa* it is again probable that only temporary relief can be obtained, while no permanent benefit can be expected as far as the tissue changes are concerned. Goldman[35] reports definite clinical improvement in one case treated with ACTH, while Stillman and Bayles[99] report successful results in another patient with continuation of the improvement for ten weeks after treatment was discontinued. The second patient, however, responded dramatically to ACTH but relapsed when therapy was discontinued. Shick et al[85] report their experience with five cases of cranial arteritis. Three of the cases of periarteritis nodosa were treated with cortisone and two with ACTH. In all cases there was permanent improvement of fever and clinical manifestations, and a gradual fall of the sedimentation rate to normal was observed. Later, however, all five patients showed partial relapses, which responded to a second course of therapy. Two cases of periarteritis died in cardiac and renal failure, despite the initial clinical improvement, and at autopsy they showed healing of the arterial lesions; but there were many visceral infarcts, apparently secondary to fibrous obliteration of the affected vessels during the healing process. Experimentally Clampit[13] reports the beneficial effects of ACTH in allergic arteritis in the rabbit.

Probably the most striking benefit has been noted in cases of *acute rheumatic fever*. Animal experiments previously noted[6] have shown that ACTH and cortisone are capable of inhibiting the tissue changes, suggesting that the clinical benefits should be marked. Herch[46] first demonstrated dramatic improvement in cases of acute rheumatic fever treated with cortisone. Within forty-eight hours there was marked clinical improvement, although the sedimentation rate did not return to normal for ten to twenty days. Thorn et al[98] confirmed the beneficial effect of ACTH and emphasized that relatively small doses of ACTH produced the same effects as large doses of cortisone. Massell[60,61,62] treated ten patients for periods of ten to fourteen days with ACTH and reports marked improvement in nine out of the ten. In five patients the rheumatic process was apparently arrested and there was no relapse one to four months after withdrawal of therapy. In two cases there was a disappearance

of the cardiac murmurs, which did not reappear after withdrawing ACTH. In some of these cases there was fluid retention, but the circulation time and vital capacity nevertheless improved. Cortisone and ACTH were used by McEwen et al[64] in three children, with good results in one case and poor results in the other two. They report a fall in the gamma globulin level and in the antistreptolysin-O titers in all patients who showed a good clinical response. Although there have been reports in which the results were not encouraging,[21,38,45] most authors feel that the improvement is striking, particularly with regard to fever and arthralgia. It is not known whether therapy will prevent chronic valvular disease, which is to be expected in about 60 per cent of the patients treated by other methods, but information of this sort can be expected with increasing follow-up periods in the cases reported. Thorn[99] demonstrates the marked reduction in cardiac size which occurred in a thirteen-year-old girl treated with ACTH. Interestingly enough, treatment could be continued for only seventy-two hours because of an inadequate supply of the hormone, but apparently the improvement was lasting.

The small number of cases reported to date would indicate that there is no definite basis for treatment of cases of *chronic glomerulonephritis* with ACTH and cortisone, except in the presence of edema when a diuresis may be beneficial.[53,55] In acute glomerulonephritis the results are encouraging but somewhat difficult to evaluate because of the small number of cases reported. Farnsworth[22,23,24] reports improvement in two cases with a rapid decrease in blood urea, nitrogen, and cholesterol accompanying permanent clinical recovery. In one of the patients there had been a brief rise in blood pressure which fell to normal during treatment. Thorn[99] reports four cases of acute nephritis treated with ACTH and feels that in spite of somewhat larger dosages than those used by Farnsworth, no benefit could be attributed directly to the ACTH therapy. They also report nine cases of chronic glomerulonephritis without significant edema, in which the results of therapy with ACTH and cortisone were disappointing, although a moderate diuresis was noted in two of the cortisone treated patients after treatment was completed. Actually in some of the cases there was increased nitrogen retention and a significant increase in blood pressure. Experimentally, Knowlton[54] and Hackel[37] have found that cortisone and ACTH do not prevent the development of cytotoxic serum nephritis in the rat, although species differences should be considered.[101]

In summary, the observations to date suggest that ACTH and cortisone alter the reactivity of the tissues to antigen-antibody combination. Whether this is purely a tissue phenomenon or whether the effect is partially or entirely due to altered antibody production is not now clear. The animal experiments recorded are contradictory, as are some of the observations in humans. It remains to be seen whether or not the observed differences reflect differences in animal species, antigen-antibody systems, or in critical evaluation of experimental data. Most of the observations, however, emphasize that a powerful inhibitory effect is produced, by whatever mechanism.

The clinical remissions observed in the collagen diseases are in some ways very encouraging, and yet it must be admitted that there is no justification for anticipating that more than temporary remissions will be produced, or that the fundamental process has been altered in any profound way. Until fundamental studies clarify the problems discussed in the first part of this review, clinical application must remain empiric and therefore not entirely satisfactory.

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## II. Hyaluronic Acid, Hyaluronidase, and the Ground Substance of the Mesenchyme with Particular Reference to the Collagen Diseases

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THE studies of Selye on disease as the manifestation of adaptation, and subsequent observations on the physiologic and therapeutic effects of adrenocorticotropic hormone and various adrenal hormones, have led to studies in physiology and biochemistry which promise to elucidate the basic mechanisms of inflammation. In the sense of "reaction to injury," inflammation is the fundamental process in disease, and any new understanding of the processes taking place is of considerable importance.

With reference to the collagen diseases it has seemed obvious[90] that the similar anatomical changes observed could not be considered to be due to the same etiological factor. At the same time a common denominator of some type could be strongly suspected.

It is the purpose of this review to summarize certain recent developments in tissue biochemistry which promise to lead us nearer to this elusive common denominator. The subject of collagen diseases with respect to ACTH and cortisone is reviewed in a concurrent publication.[91]

What is probably the earliest definitive description of a tissue factor in inflammation is provided by the observations of Durran-Reynals first reported in 1928. He noted that the injection of attenuated vaccinia virus intradermally into rabbits produced a mild lesion, whereas the same virus injected into the rabbit testis produced a very severe lesion.[23,24] Since the virus when mixed with testicular tissue extracts and injected intradermally was able to produce severe skin lesions, and since he was able to show no increased virulence in the virus *per se* when recovered from the testicular lesions, he concluded that testis tissue contained a factor which enhanced the invasiveness of the virus without altering its virulence. These observations were confirmed and extended by McLean[69] who also found that the intracutaneous injection of India ink plus testicular extract resulted in the spread of the pigment over a large area, whereas when India ink alone was injected it failed to spread away from the point of injection. He concluded that testicular extracts contained a "spreading factor" which produced an increase in tissue permeability.

A few years later investigations along apparently unrelated lines by Meyer and Palmer[83] revealed that the vitreous humor in the eyes of cattle contains an acid mucopolysaccharide which they called hyaluronic acid. This was also found in cattle aqueous humor,[84,88] human Wharton's jelly,[85] synovial fluid from cattle,[89] tumors due to leukosis virus and fowl sarcoma,[50] human malignant tumors of mesenchymal origin,[77,78] the mucoid phase of group A hemolytic streptococci[52] and in pig skin.[94] Hyaluronic acid is only one of several naturally occurring acid mucopolysaccharides, but it has received by far the greatest attention, probably because of its spectacular properties. It consists of large elongated molecules having a molecular weight of 200,000 to 500,000[51] or more, since some fractions have been prepared having extremely high viscosities. The properties of the acid mucopolysaccharides are given in several extensive reviews.[28,29,73,74,75,101] Suffice it to say here that hyaluronic acid is made

up of units of glucoronic acid and acetyl-N-glucosamine. It probably occurs in nature as a freely dissociated compound which, because it is a high molecular polybasic acid, forms compounds with proteins which precipitate at an acid pH.

The next step was the discovery of Meyer and co-workers[81,82] of an enzyme present in some strains of pneumococci which was capable of hydrolyzing hyaluronic acid. This substance, hyaluronidase, is also present in large amounts in mammalian testis extracts.[13,48,62] It has been found in various bacteria,[8,26,96] leech head extracts,[18] snake venom[27] and in the cercariae of *Schistosoma mansoni*.[60] It is believed to be necessary for the breakdown of the mucoid capsule of mammalian ova to allow penetration of the spermatozoa.[10,30,59] It has been claimed[67,79,80,93] that it is normally present in mammalian skin, although Glick feels that the methods by which it was demonstrated were unreliable.[34,36,38,104]

There is still much to be learned about the action of this enzyme which brings about hydrolysis of hyaluronic acid. The chemical structure of the substrate, the nature of the reaction, and the products of the reaction are still imperfectly understood. Particularly, the nature of the chemical linkages in hyaluronic acid is variously thought to be either two glucosidic linkages, or an ester linkage, or an anhydride linkage. Hyaluronidases are said to act on hyaluronic acid in four different ways:[76] (1) they prevent the formation of the mucin clot which separates on acidification of solutions containing protein and native hyaluronic acid, (2) they abolish the ability of hyaluronic acid to form insoluble protein salts on acidification, (3) they decrease the viscosity of solutions containing purified or native hyaluronate, and (4) they cause the opening of the glucosidic linkages as measured by the increase in reducing sugar and the increase in the color produced by Ehrlich's reagent.

Interest in this already promising field quickened with the reports of Chain and Duthie,[7,8] who found that hyaluronidase and the spreading factor were identical by showing that testis extract in very high dilutions acts as a spreading factor and also hydrolyzes hyaluronic acid. Thus until it was discovered that certain pathogenic bacteria, poisonous snakes, and insects secrete spreading factors, the increased virus invasiveness remained a matter of only academic interest. Thereafter, and with the gap between many observations bridged by the work of Chain and Duthie, it naturally developed into a field of great medical interest. Furthermore, the biological aspects fortunately could be developed on the background of sound biochemical work in the field of mesodermal polysaccharides, primarily by K. Meyer. It should be noted that mesenchymal mucopolysaccharides have deserved the most attention, although other spreading factors such as ascorbic acid, lecithin, peptones,[71] and diazotized proteins[16,17] have been discovered. The role of these other factors remains to be clarified.

Following closely upon the studies with this mucolytic enzyme system came observations which indicated that hyaluronidase inhibition can be effected both by components of the preparations studied and by other substances, and that this inhibition can be either specific or nonspecific. Hyaluronidase is itself antigenic and will provoke the formation of specific antibody, when injected into an animal. This antibody, antihyaluronidase, will inhibit the enzyme *in vitro*, and is immunologically specific so that it will inactivate only the antigenic hyaluronidase but not that from other sources.[25,47,61,63] Nonspecific inhibition is produced by an inhibitor substance in serum[42,43,44,47,64,70] as well as by various substances such as dicoumarol,[27] heparin,[70] salicylates,[40] estrogens,[100] hyaluronic acid derivatives,[45] partially depolymerized hyaluronic acid[63] and others.[34] The hyaluronidase inhibitor in mammalian sera is heat labile. A ten-minute exposure to 50° C at pH 7.4 destroys all activity,[22] with moderate loss of activity after twenty-four hours at 4° C (specific antihyaluronidase antibody is apparently much more heat stable). The agent is not dialyzable and is present in Cohn's fractions II and III. Citrated or oxalated blood is inactive, and

the addition of magnesium restores the activity of the plasma. Alcohol fractions of plasma free of magnesium are inactive.[31] This activation by magnesium ions needs further clarification.[35] It has been known that ACTH influences the level of inhibitor in blood *in vivo*, but that *in vitro* it has no effect on hyaluronidase or serum inhibitor.[35]

Glick and co-workers have shown that the level of hyaluronidase inhibitor in some blood rises during the acute phase of polyiomyelitis and falls to normal with recovery.[33] They have assayed hyaluronidase by measuring its ability to reduce the viscosity of hyaluronic acid, while inhibitor is measured by adding the serum to be tested to a standard hyaluronidase preparation and comparing the activity of this mixture to that of hyaluronidase without serum. Hyaluronidase from bovine testes and hyaluronic acid from human Wharton's jelly were used, and the inhibition was recorded in arbitrary units designated as "A." Later observations[36,38] showed a high correlation between the level of serum hyaluronidase inhibitor and certain skin conditions such as pemphigus vulgaris, pemphigus foliaceous, disseminated lupus erythematosus (higher during the acute than in the subacute and chronic stage), syphilis, erythema multiforme, erythema nodosum, chickenpox, Kaposi's varicelliform eruption, and herpes zoster. In smallpox vaccination with primary takes the level of serum hyaluronidase inhibitor rose between the tenth and thirteenth day, coinciding with the height of the reaction. Subjects showing accelerated reactions tended to show an earlier rise in the inhibitor titer. Most of the subjects showing immune reactions had no significant rise in serum inhibitor. It must be emphasized that the inhibitor response is nonspecific in that it occurs with a wide variety of infectious agents of bacterial and viral origin.[37]

The connection between collagen diseases and the foregoing considerations becomes obvious in the consideration that hyaluronic acid is a constituent of the ground substance of the connective tissue. This amorphous substance is supposed to have a gel-like structure with properties which have been the subject of several important reviews.[4,9,14,28,75] According to Schade,[97] this amorphous component of connective tissue is susceptible to changes in pH, as are collagen fibers. He proposed that the ground substance and the collagen fibers acted as a two-colloid system, reacting in a general way in opposite directions to changes in pH and ionic strength.

Altshuler and Angevine[1] have utilized the metachromatic properties of acid mucopolysaccharides in an investigation of pathogenesis of fibrinoid. Fibrinoid refers to a physiochemical change in connective tissue resulting in the formation of an eosinophilic material having the appearance of fibrin but with only some of its characteristics. Fibrinoid degeneration has been noted in rheumatic fever,[56] periarteritis nodosa,[39] scleroderma,[5,65,95] experimentally produced hypersensitivity lesions,[32,55,99] disseminated lupus erythematosus,[53,54] and other collagen diseases,[90] and for this reason Altshuler and Angevine's studies are extremely important.

As reviewed by Bohrmann,[3] there have been many theories about this interesting degenerative change, and suggestions which have been made include inspissation of fibrin *per se*,[15,72] necrosis of collagen,[56] and coagulation of the ground substance.[53] In the formation of the Aschoff nodule, Talalaeff[102] described the early formation of "mucinous edema" and then of a fine fibrillar structure, which later forms granular masses.

Knepper[57] showed that there is an increase in tissue pH during the Arthus reaction, and this alkalinity during allergic reactions has been otherwise noted.[103,105] Since in alkaline solutions acid mucopolysaccharides swell,[97] it seemed likely to Altshuler and Angevine[1] that the formation of fibrinoid depended in some way on the reaction of acid mucopolysaccharides. They studied, among others, tissue from cases of rheumatic fever, rheumatoid arthritis, disseminated lupus erythematosus, and periarteritis nodosa. On the basis of (1) metachromatic staining, (2) absence of meta-

chromasia following digestion of the tissue with hyaluronidase, and (3) the temporal, spatial, and configurational relationships between the metachromatic material and fibrinoid material, they concluded that the ground substance of the connective tissue is the only constant anatomic element in its formation. Since metachromasia could be demonstrated by toluidine blue, they felt that the reaction involved an alkaline protein.

In a later paper[2] these observations were extended and they concluded that (1) acid mucopolysaccharides are frequently found in subacute and chronic serous inflammation, (2) acid mucopolysaccharides formation cannot be correlated with any particular extrinsic agent, (3) various etiologic agents may have either a general or a local effect, (4) tissues vary in their ability to form acid mucopolysaccharides, (5) acid mucopolysaccharides may occur in tissues or lesions whose energy metabolism is characterized by increased glycolysis, (6) acid mucopolysaccharides may participate in the formation of fibrinoid, sclerotic, hyaline, and amyloid material, and connective tissue fibers, and (7) acid mucopolysaccharides formation may occur with or without cellular proliferation.

They suggest that the following physicochemical reactions of acid mucopolysaccharide (AMP) may take place in the formation of degenerative lesions:

1. Protein reacting as a base + AMP → protein–AMP complex.[86]
2. Complex-protein + AMP → protein–AMP complex + liberated group, e.g., cephalin-protein + AMP → protein–AMP complex + cephalin.[11,12]
3. Hydrophilic colloid (dispersed) + AMP → hydrophilic colloid (flocculent) + AMP.[19]
4. Colloid + AMP → colloid—AMP (coacervate).[6,58]
5. Carbohydrate + primary or secondary amine → nitrogen glycoside.[49]

We are led to the conclusion that an understanding of the reactions of the ground substance has far-reaching implications. While the emphasis has shifted from cellular factors to extracellular factors, one does not of course exclude the other, as the ultimate understanding must include both aspects of tissue physiology. With respect to collagen diseases it emphasizes more than ever the nonspecific nature of the tissue changes which have been so often noted and considered pathognomonic.

It has been suggested that the antiarthritic activity of cortisone is related to its antihyaluronidase activity.[98] However, Hechter[46] reports that cortisone fails to exhibit significant antihyaluronidase activity when tested in a manner which measures enzyme activity unequivocally. He finds that cortisone in concentrations of 10 to 100 micrograms/cc was unable to influence hyaluronidase activity *in vitro,* while in rabbit skin it failed to influence the early spreading of an indicator. Opsahl[92] has shown that adrenal cortical extract diminished the spread of dye in rabbit skin. Adrenalectomy, on the other hand, produced a marked increase in spread which could be neutralized by adrenal cortical extract.

R. L. Mayer[66] felt that antihistamines possess definite prophylactic and curative effects in experimental allergic or nonallergic inflammations of the skin, but, contrary to their antianaphylactic activity, their antidermatitic effect is not due to the antihistaminic activity but rather to their antihyaluronidase effect. Mayer and Kull[68] have shown that (1) hyaluronidase is not only a spreading factor for inert pigment indicators, but that it also increases the allergic reaction in sensitized animals, and (2) that the antihistamines markedly diminish the effect of hyaluronidase upon the diffusion of India ink as well as on the allergic reaction. The therapeutic effect of the antihistamines appears to be due to its dampening effect upon the spreading action of hyaluronidase set free during the inflammatory process.

Dorfman and Moses[21] have shown that in rheumatic fever patients treated with ACTH, the level of hyaluronidase inhibitor in the blood falls below normal levels,

a response similar to that noted in untreated patients during spontaneous recovery.[20,83] This inkling of the relation between hyaluronidase and rheumatic fever may prove to be of great importance, with possibly some relation to streptococcal hyaluronic acid and hyaluronidase. It is interesting to note also inhibition of hyaluronidase by salicylates[41,75] and, probably more important, the breakdown product, gentisic acid.[87]

It must be emphasized that reactions of the ground substance are in no way specific. The evidence to date, however, seems to suggest that basic studies of this type will provide the understanding of fundamental mechanisms necessary before therapy with ACTH and cortisone can be placed on a rational and predictable basis. This review has been presented only as a summation of what is known to date and as a background for the anticipated progress in this direction which we feel confident will take place in the future.

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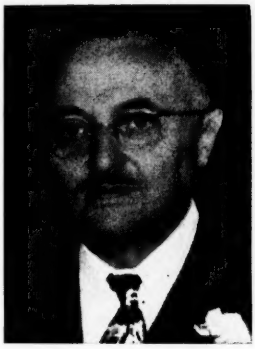
## MISSISSIPPI VALLEY MEDICAL SOCIETY

The Sixteenth Annual Meeting of the Mississippi Valley Medical Society will be held at the Pere Marquette Hotel, Peoria, Illinois, September 19, 20, 21, 1951, under the presidency of Dr. Ralph McReynolds. Over thirty clinical teachers from the leading medical schools will conduct the postgraduate assembly, planned to appeal to general practitioners. There will be over fifty exhibits, round table luncheons, and other features. No registration fee will be charged. A program may be obtained from Dr. Harold Swanberg, 209 W.C.U. Building, Quincy, Illinois.

# In Memoriam

## MATTHEW BRUNNER



Matthew Brunner, M.D., Fellow of The American College of Allergists, died of leukemia in Brooklyn, New York, on January 16, 1951, at the age of fifty-five.

He was born in New York City, December 21, 1895. He was graduated from New York University and Bellevue Medical College, receiving his M.D. degree in 1919. After serving his internship at the Jewish Hospital of Brooklyn from 1919 to 1921, he practiced allergy and medicine in Brooklyn. His postgraduate studies were taken at New York Hospital, New York Post Graduate Hospital, and Jewish Hospital of Brooklyn.

Doctor Brunner was Attending Allergist at the Jewish Hospital of Brooklyn, Jewish Sanitarium and Hospital for Chronic Diseases, and Adelphi Hospital.

He was a member of the New York Allergy Society (of which he was president at the time of his death), the American Medical Association, the American Academy of Allergy, Medical Society of the State of New York, Kings County Medical Society, and Associated Clinics of Allergy of New York City. He was author of many scientific papers in the field of allergy.

Doctor Brunner's untimely death is a great loss to the College as well as to his family and associates. The College extends deepest sympathy to family and friends.

## ANDREW ALLEN OLSON

Allen Olson, M.D., Fellow of The American College of Allergists, died May 15 at Rochester, Minnesota, following an operation for brain tumor. He was fifty-two. An allergy specialist with offices in the Brown Building, Wichita, Kansas, he had patients from a wide area. He had been in practice for twenty-five years.

Doctor Olson was born October 29, 1898, at McCracken, Kansas. He was graduated from the University of Kansas Medical School in 1925, after which he took postgraduate work at Columbia University and the University of Paris, France.

He was a member of the American Medical Association, the Kansas Medical Society, the Sedgwick County Medical Society, the International Correspondence Society of Allergists, Phi Beta Pi medical fraternity, Phi Delta Theta social fraternity, and a number of business societies in Wichita.

He is survived by his widow, Regina; two daughters, Mrs. O. J. Kaufman and Miss Peggy Olson; his mother, Mrs. N. P. Olson; a sister, Mrs. Fred George; and three brothers, Lloyd and Willard Olson and Dr. Paul Olson.

The College extends sincere condolences to the family in their time of bereavement.

# News Items

## SESSION ON ALLERGY

### One Hundredth Annual Session, American Medical Association

The Session on Allergy under the auspices of the American Medical Association met in the Renaissance Room of the Ambassador Hotel, June 13, 1951, at 2:00 p.m. The officers were Chairman Samuel M. Feinberg, Chicago, and Secretary William Sherman, New York. The Executive Committee consisted of Samuel Feinberg, Chairman, Chicago; Leon Unger, Chicago; and Fred W. Wittich, Minneapolis. The session was attended by a full-capacity house.

There was some deviation from the regular presentation of subjects as scheduled in the program. The session was opened by a round-table discussion on ACTH and cortisone in allergic diseases; the leaders were Robert A. Cooke and Marion B. Sulzberger of New York. It was stressed that these hormones proved to have great therapeutic effect in the temporary suppression of symptoms in the various allergic diseases, such as bronchial asthma, allergic dermatitis, urticaria, and drug allergies. Their use required close observation of the metabolic state of the patient to detect and control possible side effects. The effect of these drugs in allergic diseases is only temporary and not curative, so that they do not replace the need for the usual allergic management. The leaders discussed the use of these drugs in the various allergic diseases in which they have proved valuable.

Doctor Cooke pointed out that we do not know how these hormones act, because they do not remove the underlying basic factors. When the hormones are stopped, symptoms promptly return. Patients in severe status asthmaticus were treated four to seven days with ACTH, depending on the stage and the severity of the case. These hormones have a place in the therapy of vasospastic rhinitis with polypi and chronic urticaria. Recovery can be accelerated in nonseasonal rhinitis, particularly in cases where it has been impossible to determine the etiological factor, if patients are placed in a hospital and given ACTH or cortisone. Hormone therapy is tried in those cases where immunization has failed for over a year.

The oral administration of cortisone was quite as satisfactory as when administered intramuscularly and with the same results. ACTH was given intramuscularly or intravenously. The dosage was low, 80 to 100 mg at intervals of six hours, followed by diminishing amounts and intervals. In order to obtain a low, continuous effect, 10 to 20 mg of ACTH in 500-1000 cc in 5 per cent glucose solution was given at a comparatively slow rate. Doses as low as 2 to 5 mg were given. This low-dosage schedule of 100 mg of ACTH in twenty-four hours in divided doses resulted in comparatively few complications. Only two of their large series showed psychotic reactions. Some patients may develop a sensitization with edema and potassium depletion. During administration of these hormones the urine and blood pressure are carefully watched, since glycosuria may result. Potassium salts may be used in conjunction with the administration; potassium iodide serves this purpose very well. The return to normal of the blood sedimentation rate and the reduction of eosinophils to normal do not determine whether a sufficient amount of hormones has been given, so they must be administered with due caution and care.

Doctor Sulzberger reported favorable results in the use of these hormones for skin diseases such as atopic and disseminated dermatitis; contact dermatitis such as poison ivy obtained prompt relief. Cortisone was given by mouth for infantile eczema. Itching from all causes such as pruritus vulvae and pruritus ani, responded well.

Doctor Sulzberger pointed out that these hormones are good anesthetics as well as good analgesics. Drug eruptions were helped. Periarteritis nodosa was particularly benefited. Acne due to iodides and bromides was benefited, as well as fixed eruptions. There were erratic influences on the response of tuberculous lesions, which became very sensitive following the administration of ACTH.

ACTH lowers resistance to infection, and thromboses may result. Small doses of ACTH do not cause adrenal cortex degeneration. In treating the allergic dermatoses, larger doses were employed than those used for respiratory disease. Sometimes as much as 150 to 200 mg was given and then reduced to 25 mg every day or every second day.

No beneficial effects of topical application of the hormones were observed in any strength. It is a mystery why they do no good even in open lesions. There was no effect even when injected under the lesions. This may be a fundamental factor in understanding the effect of these hormones.

## FIRST INTERNATIONAL CONGRESS OF ALLERGISTS

The First International Congress of Allergists, important for trade and industry, will be held at Zurich, Switzerland, from September 23 to 29, 1951. The Congress, which will be attended by well-known physicians from all parts of the world, is being organized by the Swiss Society of Allergists and is under the patronage of the Swiss Federal Council. More than 3000 participants are expected.

The Congress will be followed by a Symposium on the "Influence of the Hypophysis and the Adrenal Cortex on Biological Reactions," arranged by the Swiss Academy of Medical Sciences.

The S. Karger Publishing Company, publishers of the *International Archives of Allergy and Applied Immunology,* official organ of the International Association of Allergists, announces the publication of a greatly enlarged Congress Number of the *International Archives,* 3000 copies of which will be issued and distributed not only to the regular subscribers, but also to the participants of the Congress. This journal publishes only original articles in German and English and is under the chief editorship of the Doctors P. Kallós, Helsingborg; W. Löffler, Zurich; and Fred W. Wittich, Minneapolis. Contributions from leading scientists all over the world will appear in this special number, and the issue following the Congress Number will include an account of the Congress, as well as all the papers read at the meeting. Both special issues will afford the reader a unique opportunity to directly contact the important and influential medical research men.

The rates for single advertisements are as follows:

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Regular advertisers in the periodicals published by S. Karger Publishing Company are allowed the usual discount. Detailed information will be gladly furnished upon request. Write to S. Karger, Ag., Holbeinstrasse 22, Basel, Switzerland.

## AAPS PROGRAM

The Association of American Physicians and Surgeons, Inc., held its 1951 Delegates Interim Meeting, April 20-21, at the LaSalle Hotel, Chicago. The AAPS is a nonprofit organization composed of many physicians from every state in the union, not for the presentation of scientific programs but for a program of representing and protecting the interests of physicians in the socio-economic aspects of medical practice and for a program of freedom education for all physicians, as well as a tax economy campaign. The Association continues its affiliation with the All-American Con-

ference to combat Communism, which was organized last year by the American Legion. The Association issues copies of the *AAPS News Letter* each month, not only to its members but to those who subscribe to it. These *News Letters* clearly set forth, without any propaganda approach, proposed bills and those which have been passed by Congress when advancing Mr. Ewing's program for socialized medicine. It is appalling how insidiously these bills have been passed comparatively unnoticed. Many physicians feel secure, thinking that the program for socialized medicine is being defeated. It is just the contrary, and it will not be long before we have socialized medicine if these "fringe bills" continue to be sneaked through because of the indifference of the profession in petitioning their Congressmen.

The Association is now sending one copy of the *AAPS News Letter* each month to all of the house chapters of the Phi Chi medical fraternity. These subscriptions are paid for by the Eli Lilly Company of Indianapolis. This is one of the first steps in the Association's program to provide each intern and medical student with regular issues of the *News Letter.*

Eighteen state medical societies and 300 county medical societies have endorsed the AAPS program. Endorsement by a society does not commit any individual to membership.

A very ambitious program has been planned for the next year. Essay contests will be conducted in various public schools with prizes ranging from $1000 to $5 for the best essay opposing socialized medicine. For further information write to the executive secretary, Harry E. Northam, 360 North Michigan Avenue, Chicago 1, Illinois.

## ACA COMMITTEES

At the last meeting of the Board of Regents, a Committee on Dermatologic Allergy was established. Its aims are to improve the dermatologic service to the College and to the ANNALS OF ALLERGY, and also to assist in the preparation of the program for the Annual Congress and the educational courses. Any member who would like to co-operate with the committee or present suggestions is invited to contact the chairman, Dr. Stephan Epstein, Marshfield, Wisconsin.

Chairman of the Pediatrics Committee is Dr. Bret Ratner, 50 East 78th Street, New York City. Dr. Harold A. Abramson, 133 East 58th Street, New York City, is chairman of the Committee on Psychosomatics. The newly activated Publicity Committee is headed by Dr. William Kaufman, 540 Brooklawn Avenue, Bridgeport, Connecticut. The personnel of all these committees will appear on a page near the masthead in the next issue of the ANNALS.

## AMERICAN ACADEMY OF ALLERGY

Dr. Horace L. Baldwin, president of The American Academy of Allergy, has sent a letter dated June 20 to all Fellows and members of the Academy of Allergy, notifying them that the next meeting of the Academy will be held in Chicago at the Hotel Sherman, Monday, Tuesday, and Wednesday, February 18, 19, and 20, 1952.

All members and Fellows of the Academy are invited to make suggestions and plan to submit papers, if possible. The title and an abstract not exceeding 200 words should be furnished in quadruplicate to the Executive Office, 208 East Wisconsin Avenue, Milwaukee 2, Wisconsin, before October 15. The essayist is urged to indicate the length of his paper, whether five, ten, or fifteen minutes. In general, papers should be limited to ten minutes or less. Any exceptions to this rule should be noted when the abstract is submitted.

As many papers as possible are desired. Completed papers may be submitted to the

Editor of *Journal of Allergy*, Dr. W. B. Sherman, 60 East 58th Street, New York 22, New York; and all papers read at the meeting must be submitted to the Editor for publication in the *Journal*.

### CONNECTICUT ALLERGY SOCIETY

The Connecticut Allergy Society held its spring meeting in conjunction with the annual meeting of the Connecticut State Medical Society on Wednesday, May 2, at the Stratford High School. Dr. Harold A. Abramson, Chief of the Allergy Service at Mt. Sinai Hospital, New York City, and President of The American College of Allergists, addressed the group and its guests on "Practical Somatic and Psychiatric Therapy of Asthma."

### SOUTHWEST ALLERGY FORUM

The Southwest Allergy Forum will hold its 1952 meeting at the Baker Hotel, 1400 Commerce, Dallas, Texas, March 2, 3, 4. There will be a stimulating scientific program, adequate social entertainment, and Southwestern hospitality. Each member is urged to submit a paper for presentation. An abstract of the paper should be submitted to the Secretary-Treasurer, Dr. James Holman, 1405 Medical Arts Building, Dallas, Texas, by December 1, 1951. The abstract should not exceed 200 words and should be furnished in duplicate.

### PRACTICE AVAILABLE

Because of the untimely death of Allen Olson, M.D., F.A.C.A., there is now no allergist in the city of Wichita, Kansas. Doctor Olson's practice of approximately 750 patients is available for a young, well-trained allergist. Information may be obtained from Mrs. Allen Olson, Suite 804, Brown Building, Wichita, Kansas.

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Alan G. Cazort, M.D., F.A.C.A., announces the association of Thomas G. Johnston, M.D., in the practice of allergy, July 1, 1951, at 1425 West Seventh Street, Little Rock, Arkansas.

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## RECURRENT ATTACK OF ASTHMA

*(Continued from Page 512)*

younger. For me the big troubles are big. But they are there and I have to stand them. The little troubles fortunately aren't too big any more.

"I seem more in proportion. Yes, that's a good word for it. More in proportion. That's what I am."

This illustrates a case where the physician has a psychotherapist working right in his office. However, it illustrates, too, the needs that the asthmatic child has for trusting an older person and for expressing his fears and his anger to this person. These needs each physician can help fulfill in his own unique way.

*201 South Lasky Drive*

# BOOK REVIEWS

THE AMERICAN ILLUSTRATED MEDICAL DICTIONARY. 22nd edition. By W. A. Newman Dorland, M.D. 1736 pages, many illustrations, some in color. Price $10.00. Philadelphia: W. B. Saunders Company, 1951.

This revised, thumb-indexed volume with flexible cover has just been received. The 22nd edition of this medical dictionary which has been fifty years in existence gives users the most complete coverage possible of the fast-growing medical vocabulary. The valuable new features include a preliminary article on fundamentals of medical etymology by Prof. Lloyd W. Daly of the Department of Classical Studies of the University of Pennsylvania, and a table of modern drugs and dosage compiled by Dr. Austin Smith, Editor of the J.A.M.A. The table of drugs, based on *New and Nonofficial Remedies,* lists drugs according to their therapeutic purpose or effect, making it a convenient source of reference.

A long list of prominent authorities who are contributors is given, including many in the Mayo Clinic and Foundation, especially Drs. John R. Miner and James R. Eckman.

The sections defining muscles, nerves, and blood vessels contain extensive tables and illustrated plates, similar to a textbook on anatomy. There are excellent historical sketches, with illustrations, of the pioneers in medicine. The table of tests in this new edition is very comprehensive.

This edition appears in new typography and a new design. It is a complete dictionary of terms used in medicine, surgery, dentistry, pharmacy, chemistry, nursing, veterinary science, biology, and medical biography, with their pronunciation, derivation, and definition. When retaining the old and embracing the new, the editors are to be congratulated on keeping the volume within the limits required by convenience of usage. It is a book that is essential for the desk of every physician and medical student.

SOMATIC AND PSYCHIATRIC TREATMENT OF ASTHMA. Harold A. Abramson, M.D., Editor; 34 contributors. 751 pages, numerous figures. Price $11.00. Baltimore: The Williams and Wilkins Company, 1951.

This broad approach to the therapy of the most distressing and crippling allergic disease is the first volume of this nature. It is a clear, understandable volume which co-ordinates our present knowledge of the allergic nature of asthma. With an understanding of psychodynamics essential to certain methods of the therapy of asthma, Doctor Abramson has successfully established suitable therapeutic procedures based upon a closer correlation of two independently developed fields: namely, the theoretical and practical bases of immunology and psychotherapy. Besides the chapters contributed by the editor, there are thirty-three other contributors selected because of their particular knowledge gathered through research and filled in with experience. This group has presented

1. The physiological bases of the asthmatic syndrome;
2. The psychodynamics of respiration;
3. The mechanisms of the underlying experimental production of asthma in animals and in man;
4. The chemical and physical nature of certain typical common extrinsic causes of inhalant asthma;
5. The evaluation of methods of immunotherapy;

6. Special aspects of applied pharmacology, endocrinology, dietotherapy, and surgery in the management of the patient;
7. The relationship of the parents with the asthmatic child;
8. The usefulness of psychotherapy in general for the asthmatic patient.

The editor purposely allowed a certain amount of repetition in order to obtain similar data from different points of view.

Doctor Abramson, internationally known for his contributions to physiology, allergy, and psychiatry, is particularly fitted to aid those embracing the immunologic viewpoint to understand psychodynamic factors, and to aid the psychiatrist to appreciate the immunologic phases of asthma. He stresses the point that "pure psychogenic asthma" is either rare or nonexistent but that prolonged mild asthma or status asthmaticus is frequently intensified by personality conflicts which may be benefited by psychotherapy.

The book is divided into six parts containing thirty-five chapters, with references at the end of each. Most of the chapters are well written. Some of the outstanding chapters are by the author-editor, particularly those on the nature of pollen allergens, aerosol therapy of the lungs and bronchi, and psychodynamic pharmacology in the therapy of asthma. Of particular note is the chapter by Rimington of England on the chemical nature of dust allergen. The chapters on the basic concepts are well balanced by very practical articles, including prescriptions, pediatric allergy, dietotherapy, the use of hormones, the therapeutic inhalation of gases, bronchoscopy, otolaryngology, and surgical treatment.

BLOOD GROUPS IN MAN. By R. R. Race and Ruth Sanger, Medical Research Council, Blood Group Research Unit, Lister Institute, London. 290 pages. Price $6.50. Springfield, Ill.: Charles C Thomas, 1951.

A much-needed comprehensive presentation of the status of our knowledge of blood groups has been made available by the authors, who have acquired international reputation from their important contributions to this field. Thus it need hardly be stated that it is a highly competent and reliable source of information, indeed without competition at the present time in this rapidly developing specialty. As such it will be of great value to all interested in the many fascinating theoretical and practical aspects of blood serology, a value enhanced by the lucidity and succinctness with which this complex matter is presented. A judicious selection of references further adds to the usefulness of the book.

Although the subject does not immediately concern those engaged in the specialty of clinical allergy, the study of this book should reward every allergist interested in the larger aspects and the future development of his field. Particularly the genetic implications of research in blood antigens and the ingenious methods for demonstrating antibody-antigen reactions developed during this work should be highly stimulating to our colleagues.

SERUM SICKNESS. By C. Frh. von Pirquet, M.D., and Bela Schick, M.D. (translated by Schick). 130 pages, numerous tables and charts. Price $3.50. Baltimore: The Williams and Wilkins Company, 1951.

Forty-five years have elapsed since *Serumkrankheit* appeared, in which von Pirquet and Schick recorded their observations and upon which our knowledge of allergy is based. The original volume, published in 1905, has been out of print for some years and copies are rare. Also, of course, it was written in German, which put it beyond the reach of many potential readers. Doctor Schick has succeeded in translating this classic into fluent English that retains the flavor of the original language.

It is a great satisfaction to Doctor Schick to observe that not only were their original clinical observations complete but also their theoretical ideas have stood the test of time. Many problems mentioned in the original volume were later elaborated by Pirquet, such as vaccination. His tuberculin test marks his genius as the father of all skin testing. Our knowledge of allergic diseases has its origin in the observations of serum sickness which contain passive transfer and serum sickness "in reverse."

For those who have never had the privilege of reading the original volume, a brief description of the contents follows. There are three chapters: Chapter 1 describes succinctly the clinical aspects of serum sickness; Chapter 2, the reinjection, describes the immediate reactivity, experimental studies, accelerated reactivity, clinical symptoms, and the diagnostic importance of immediate and accelerated reactivity; and Chapter 3 contains the subsequently proven theories of serum sickness, antibody reaction *in vitro,* acquired hypersensitiveness, et cetera.

The publishers are to be congratulated for persuading the author of the translation of this basic information to make it available to all physicians and students interested in allergy.

ALLERGY: FACTS AND FANCIES. By Samuel M. Feinberg, M.D., Northwestern University Medical School, Chicago; with a preface by Austin Smith, M.D., Editor, J.A.M.A. 173 pages. Price $2.50. New York: Harper and Brothers, 1951.

This little volume is intended to furnish in simple language what the allergic patient should know. Modern laboratory methods of diagnosis, etiological factors, and a proper evaluation of the latest methods of medication, including ACTH and cortisone and the antihistamines, are clearly presented. Many books of this nature are written with a spectacular approach which sacrifices the actual truth and becomes misleading. Doctor Feinberg reports the necessary information for the patient who really wants to know the facts about allergy when co-operating with the physician in the management of his case. The book is a condensation of the author's popular *Allergy in Practice,* Chicago: Year Book Publishers. Physicians and public health workers will find this guide for patients a great help.

# Magazine Reviews

## JOURNAL OF HUMAN ECOLOGY

The Weather Science Foundation announces the inauguration of a new scientific journal, the *Journal of Human Ecology,* which began in January, 1951.

The new journal is devoted to original research and reviews in connection with the effect of environment on human beings. This includes the effect of environment on human structure, physiological processes, health, behavior, personality, intelligence, and mental reactions, as well as the relationship of environmental factors—geographical, meteorological, and climatic—to business trends and price moves. Any study of cyclic behavior pertaining directly or indirectly to human welfare, or studies of the effect of artificial climates on man and animals, would fall within the scope of the Journal, as well as studies relating historical events to climatic changes.

It is believed that the Journal will be of interest and value to psychologists, animal and plant ecologists, medical climatologists, economists, sociologists, political scientists, and historians, even those in the humanities and the arts who are interested in the effect of environmental forces upon cultural achievement.

The Journal is offset printed at Crystal Lake, Illinois. Separate articles will be issued in loose-leaf form as monographs as soon as received and accepted. Ap-

propriate binders for filing will be sent to subscribers. All are invited to contribute papers. The point of view may be that of either the pure or the applied scientist. No specific length is required. The Journal is in no sense a trade journal or an advertising project. Its purpose is to offer a medium for the publication of an ever-growing amount of research in human ecology.

Correspondence regarding papers should be addressed to Raymond H. Wheeler, Editor, Babson Institute of Business Administration, Babson Park 57, Massachusetts. Correspondence regarding subscriptions should be addressed to the Managing Editor, Sydney D. Thompson, Weather Science Foundation, Crystal Lake, Illinois. A special subscription rate of $15 is offered to members of college and university faculties or to those doing individual research, and to college and university libraries. To others the standard subscription rate is $25 per year.

### INDUSTRIAL HEALTH MONTHLY

The Federal Security Agency, Public Health Service, announces a change in the name of their official monthly publication, known for ten years as The Industrial Hygiene News letter. With the April, 1951, issue, the name became *Industrial Health Monthly.*

The purpose and policies will remain the same. It will continue to serve as a medium for the interchange of news among state and local industrial hygiene staffs. In keeping with previous practice, material will be selected for its value to industrial managers, physicians, nurses, chemists, and others, as well as governmental industrial hygienists.

It is available for $1 a year (domestic mailing) or $1.25 (foreign mailing) from the Government Printing Office, Washington 25, D. C.

### ANTIBIOTICS AND CHEMOTHERAPY

We take pleasure in announcing the appearance of Volume 1, Number 1, April, 1951, of *Antibiotics and Chemotherapy,* published by the Washington Institute of Medicine. Published monthly, it is a 106-page magazine with numerous tables, figures, and photographs. The subscription price is $10 for one year, $22.50 for three years. The address is Washington Institute of Medicine, 667 Madison Avenue, New York 21, N. Y.

The ever-increasing scope of the research and clinical developments in the fields of antibiotics, hormones, and chemotherapeutics has rather definitely indicated the need for a specialized publication wherein papers reporting the newer developments and applications might be promptly published. In the first issue there are presented fifteen papers, eleven abstracts, and three book reviews.

An introduction by Selman A. Waksman, Ph.D., Professor of Microbiology, Rutgers University, defines this new field. Harry F. Dowling, M.D., University of Illinois, gives the present status of antibiotic therapy. There is an excellent historical chapter by Edward C. Kendall of the Mayo Clinic on the development of cortisone as a therapeutic agent. Other features are chapters on treatment of scrub typhus by Charles A. Bailey, et al; on the effect of different levels of aureomycin with and without vitamin $B_{12}$ on growing-fattening swine; on growth response of swine fed penicillin; on a plate method of antibiotic assay with *Mycobacterium tuberculosis* 607 and *Brucella abortus;* terramycin in the treatment of yaws; and Chloromycetin in the treatment of yaws.

There are twelve abstracts of recent publications of the international medical literature on various antibiotics as well as excellent book reviews. The paper stock is of good quality, the photographs very clear, and the print readable.

The editors request that appropriate papers be submitted for consideration. Those interested may write the publisher for a partial list of papers accepted for future publication.

## *Index to Advertisers*